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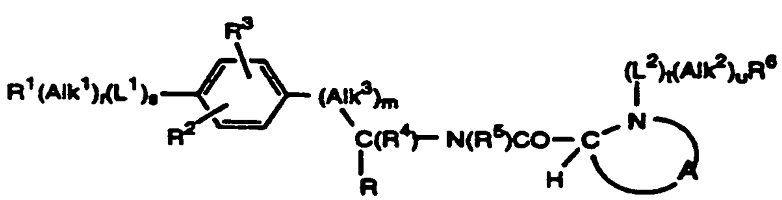

(1)

(57) Abstract

Phenylalanine derivatives of formula (1) are described, in which L^1 is a linker atom or group; A is a chain $-[C(R^7)(R^8)]_pY[C(R^9)(R^{10})]_q-$ in which Y is a sulphur atom or a $-S(O)-$ or $-S(O)_2-$ group, R^7, R^8, R^9 and R^{10}, which may be the same or different, is each a hydrogen atom or a straight or branched alkyl or optionally substituted aromatic group, or R^7 and R^8 together with the carbon atom to which they are attached, or R^9 and R^{10} together with the carbon atom to which they are attached, each forms a C_{3-7}cycloalkyl group, and p and q, which may be the same or different, is each zero or an integer 1 or 2, provided that when one of p or q is zero the other is an integer 1 or 2; L^2 is a linker group selected from $-C(O)-$, $-C(O)O-$, $-C(S)-$, $-S(O)_2-$, $-CON(R^{11})-$, {where R^{11} is a hydrogen atom or a straight or branched alkyl group}, $-CSN(R^{11})-$, $-SON(R^{11})-$ or $SO_2N(R^{11})-$; R is a carboxylic acid or a derivative thereof; and the salts, solvates and hydrates thereof. The compounds are able to inhibit the binding of α_4 integrins to their ligands and are of use in the prophylaxis and treatment of immune or inflammatory disorders.

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PHENYLALANINE DERIVATIVES

This invention relates to a series of phenylalanine derivatives, to compositions containing them, to processes for their preparation, and to their use in medicine.

Over the last few years it has become increasingly clear that the physical interaction of inflammatory leukocytes with each other and other cells of the body plays an important role in regulating immune and inflammatory responses [Springer, T A. Nature, 346, 425, (1990); Springer, T. A. Cell 76, 301, (1994)]. Many of these interactions are mediated by specific cell surface molecules collectively referred to as cell adhesion molecules.

The adhesion molecules have been sub-divided into different groups on the basis of their structure. One family of adhesion molecules which is believed to play a particularly important role in regulating immune and inflammatory responses is the integrin family. This family of cell surface glycoproteins has a typical non-covalently linked heterodimer structure. At least 14 different integrin alpha chains and 8 different integrin beta chains have been identified [Sonnenberg, A. Current Topics in Microbiology and Immunology, 184, 7, (1993)]. The members of the family are typically named according to their heterodimer composition although trivial nomenclature is widespread in this field. Thus the integrin termed $\alpha4\beta1$ consists of the integrin alpha 4 chain associated with the integrin beta 1 chain, but is also widely referred to as Very Late Antigen 4 or VLA4. Not all of the potential pairings of integrin alpha and beta chains have yet been observed in nature and the integrin family has been subdivided into a number of subgroups based on the pairings that have been recognised [Sonnenberg, A. *ibid*].

The importance of cell adhesion molecules in human leukocyte function has been further highlighted by a genetic deficiency disease called Leukocyte Adhesion Deficiency (LAD) in which one of the families of leukocyte integrins is not expressed [Marlin, S. D. *et al* J. Exp. Med. 164, 855 (1986)]. Patients with this disease have a reduced ability to recruit

leukocytes to inflammatory sites and suffer recurrent infections which in extreme cases may be fatal.

The potential to modify adhesion molecule function in such a way as to beneficially modulate immune and inflammatory responses has been extensively investigated in animal models using specific monoclonal antibodies that block various functions of these molecules [e.g. Issekutz, T. B. J. Immunol. 3394, (1992); Li, Z. *et al* Am. J. Physiol. 263, L723, (1992); Binns, R. M. *et al* J. Immunol. 157, 4094, (1996)]. A number of monoclonal antibodies which block adhesion molecule function are currently being investigated for their therapeutic potential in human disease.

One particular integrin subgroup of interest involves the $\alpha 4$ chain which can pair with two different beta chains $\beta 1$ and $\beta 7$ [Sonnenberg, A. *ibid*]. The $\alpha 4 \beta 1$ pairing occurs on many circulating leukocytes (for example lymphocytes, monocytes and eosinophils) although it is absent or only present at low levels on circulating neutrophils. $\alpha 4 \beta 1$ binds to an adhesion molecule (Vascular Cell Adhesion Molecule-1 also known as VCAM-1) frequently up-regulated on endothelial cells at sites of inflammation [Osborne, L. Cell, 62, 3, (1990)]. The molecule has also been shown to bind to at least three sites in the matrix molecule fibronectin [Humphries, M. J. *et al*. Ciba Foundation Symposium, 189, 177, (1995)]. Based on data obtained with monoclonal antibodies in animal models it is believed that the interaction between $\alpha 4 \beta 1$ and ligands on other cells and the extracellular matrix plays an important role in leukocyte migration and activation [Yednock, T. A. *et al*, Nature, 356, 63, (1992); Podolsky, D. K. *et al*. J. Clin. Invest. 92, 373, (1993); Abraham, W. M. *et al*. J. Clin. Invest. 93, 776, (1994)].

The integrin generated by the pairing of $\alpha 4$ and $\beta 7$ has been termed LPAM-1 [Holzmann, B and Weissman, I. EMBO J. 8, 1735, (1989)] and like $\alpha 4 \beta 1$, binds to VCAM-1 and fibronectin. In addition, $\alpha 4 \beta 7$ binds to an adhesion molecule believed to be involved in the homing of leukocytes to mucosal tissue termed MAdCAM-1 [Berlin, C. *et al*, Cell, 74, 185, (1993)]. The interaction between $\alpha 4 \beta 7$ and MAdCAM-1 may also be important at

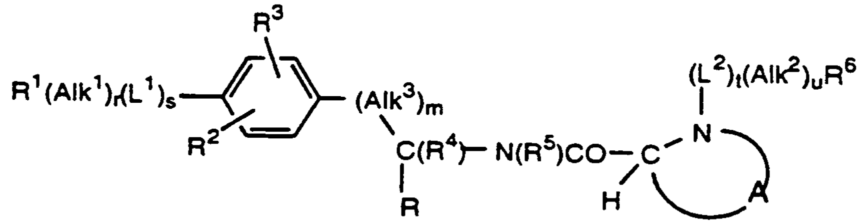
sites of inflammation outside of mucosal tissue [Yang, X-D. *et al*, PNAS, 91, 12604 (1994)].

Regions of the peptide sequence recognised by $\alpha4\beta1$ and $\alpha4\beta7$ when they bind to their ligands have been identified. $\alpha4\beta1$ seems to recognise LDV, IDA or REDV peptide sequences in fibronectin and a QIDSP sequence in VCAM-1 [Humphries, M. J. *et al*, *ibid*] whilst $\alpha4\beta7$ recognises a LDT sequence in MAdCAM-1 [Briskin, M. J. *et al*, J. Immunol. 156, 719, (1996)]. There have been several reports of inhibitors of these interactions being designed from modifications of these short peptide sequences [Cardarelli, P. M. *et al* J. Biol. Chem. 269, 18668, (1994); Shroff, H. N. Bioorganic. Med. Chem. Lett. 6, 2495, (1996); Vanderslice, P. J. Immunol. 158, 1710, (1997)]. It has also been reported that a short peptide sequence derived from the $\alpha4\beta1$ binding site in fibronectin can inhibit a contact hypersensitivity reaction in a trinitrochlorobenzene sensitised mouse [Ferguson, T. A. *et al*, PNAS 88, 8072, (1991)].

Since the alpha 4 subgroup of integrins are predominantly expressed on leukocytes their inhibition can be expected to be beneficial in a number of immune or inflammatory disease states. However, because of the ubiquitous distribution and wide range of functions performed by other members of the integrin family it is very important to be able to identify selective inhibitors of the alpha 4 subgroup.

We have now found a group of compounds which are potent and selective inhibitors of $\alpha4$ integrins. Members of the group are able to inhibit $\alpha4$ integrins such as $\alpha4\beta1$ and/or $\alpha4\beta7$ at concentrations at which they generally have no or minimal inhibitory action on α integrins of other subgroups. The compounds are thus of use in medicine, for example in the prophylaxis and treatment of immune or inflammatory disorders as described hereinafter.

Thus according to one aspect of the invention we provide a compound of formula (1)



(1)

wherein

R^1 is a hydrogen atom or an optionally substituted cycloaliphatic, polycycloaliphatic, heterocycloaliphatic, polyheterocycloaliphatic, aromatic or heteroaromatic group;

Alk^1 and Alk^2, which may be the same or different, is each an optionally substituted aliphatic or heteroaliphatic chain;

L^1 is a linker atom or group;

r, s, t and u is each zero or an integer 1;

Alk^3 is a straight or branched alkylene chain;

m is zero or an integer 1;

R^4 is a hydrogen atom or a methyl group;

R^5 is a hydrogen atom or a straight or branched alkyl group;

A is a chain $-[C(R^7)(R^8)]_pY[C(R^9)(R^{10})]_q-$ in which Y is a sulphur atom or a -S(O)- or $-S(O)_2-$ group, R^7, R^8, R^9 and R^{10}, which may be the same or different, is each a hydrogen atom or a straight or branched alkyl or optionally substituted aromatic group, or R^7 and R^8 together with the carbon atom to which they are attached, or R^9 and R^{10} together with the carbon atom to which they are attached, each forms a C_{3-7}cycloalkyl group, and p and q, which may be the same or different, is each zero or an integer 1 or 2, provided that when one of p or q is zero the other is an integer 1 or 2;

L^2 is a linker group selected from -C(O)-, -C(O)O-, -C(S)-, $-S(O)_2-$, $-CON(R^{11})-$, [where R^{11} is a hydrogen atom or a straight or branched alkyl group], $-CSN(R^{11})-$, $-SON(R^{11})-$ or $SO_2N(R^{11})-$;

R^2 and R^3, which may be the same or different is each an atom or group $-L^3(CH_2)_pL^4(R^{2a})_q$ in which L^3 and L^4 is each a covalent bond or a linker atom or group, p is zero or the integer 1, q is an integer 1, 2 or 3 and R^{2a} is a hydrogen or halogen atom or a group selected from straight or branched alkyl, $-OR^{12}$ [where R^{12} is a hydrogen atom or an optionally

substituted straight or branched alkyl group], $-SR^{12}$, $-NR^{12}R^{13}$, [where R^{13} is as just defined for R^{12} and may be the same or different], $-NO_2$,-CN, $-CO_2R^{12}$, $-SO_3H$, $-SO_2R^{12}$, $-OCO_2R^{12}$, $-CONR^{12}R^{13}$, $-OCONR^{12}R^{13}$, $-CSNR^{12}R^{13}$, $-COR^{12}$, $-N(R^{12})COR^{13}$, $N(R^{12})CS^{13}$, $-SO_2N(R^{12})(R^{13})$, $-N(R^{12})SO_2R^{13}$, $-N(R^{12})CONR^{13}R^{14}$ [where R^{14} is a hydrogen atom or an optionally substituted straight or branched alkyl group], $-N(R^{12})CSNR^{13}R^{14}$ or $-N(R^{12})SO_2NR^{13}R^{14}$;

R is a carboxylic acid or a derivative thereof;

R^6 is a hydrogen atom or an optionally substituted cycloaliphatic, polycycloaliphatic, heterocycloaliphatic, polyheterocycloaliphatic, aromatic or heteroaromatic group, provided that:

(1) when $R^1(Alk^1)_r(L^1)_s$- is $R^1(Alk^1)_rO$-, $R^1(Alk^1)_rC(O)O$-, $R^1(Alk^1)_rNHC(O)O$- or $R^1(Alk^1)_rS(O)_2O$-, [in which R^1 is a hydrogen atom or an optionally substituted aromatic group and Alk^1 is an optionally substituted alkyl group] and $R^6(Alk^2)_u(L^2)_t$- is $R^6(Alk^2)_uCO$-, $R^6(Alk^2)_uC(O)O$-, $R^6(Alk^2)_uNHCO$- or $R^6(Alk^2)_uS(O)_2$- [in which Alk^2 is an optionally substituted alkyl chain], then R^6 is an optionally substituted cycloaliphatic, polycycloaliphatic, heterocycloaliphatic or heteroaromatic group; and

(2) Alk^2,when present is not a $-(CH_2)_nS$-, $-(CH_2)_nSS$- or $-(CH_2)_nSC(O)$- chain, where n is an integer 1, 2 or 3;

and the salts, solvates and hydrates thereof.

It will be appreciated that compounds of formula (1) may have one or more chiral centres. Where one or more chiral centres is present, enantiomers or diastereomers may exist, and the invention is to be understood to extend to all such enantiomers, diasteromers and mixtures thereof, including racemates. Formula (1) and the formulae hereinafter are intended to represent all individual isomers and mixtures thereof, unless stated or shown otherwise.

In the compounds of formula (1), derivatives of the carboxylic acid group R include carboxylic acid esters and amides. Particular esters and amides include $-CO_2R^{12}$ and $CONR^{12}R^{13}$ groups as described herein.

Alk^3 in the compounds of the invention may be for example a straight or branched C_{1-3}alkylene chain. Particular examples include $-CH_2-$, $-CH(CH_3)-$ and $-(CH_2)_2-$.

When each of R^{2a}, R^5, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13} and/or R^{14} in the compounds of formula (1) is a straight or branched alkyl group it may be a straight or branched C_{1-6}alkyl group, e.g. a C_{1-3}alkyl group such as a methyl or ethyl group. When the R^{12}, R^{13} and/or R^{14} group is optionally substituted, the substituent may be selected for example from one, two, three or more of the optional substituents described below in relation to the aliphatic groups represented by Alk^1.

When in the compounds of the invention L^1, L^3 and/or L^4 is present as a linker atom or group it may be any divalent linking atom or group. Particular examples include -O- or -S- atoms or -C(O)-, -C(O)O-, -C(S)-, -S(O)-, $-S(O)_2-$, $-N(R^{11})-$ [where R^{11} is as defined previously], $-CON(R^{11})-$, $-OC(O)N(R^{11})-$, $-CSN(R^{11})-$, $-N(R^{11})CO-$, $-N(R^{11})C(O)O-$, $-N(R^{11})CS-$, $-S(O)N(R^{11})-$, $-S(O)_2N(R^{11})-$, $-N(R^{11})S(O)-$, $-N(R^{11})S(O)_2-$, $-N(R^{11})CON(R^{11})-$, $-N(R^{11})CSN(R^{11})-$, $-N(R^{11})SON(R^{11})-$ or $-N(R^{11})SO_2N(R^{11})-$ groups. Where the linker group contains two R^{11} substituents, these may be the same or different.

When Alk^1 and/or Alk^2 compounds of formula (1) is an optionally substituted aliphatic chain it may be an optionally substituted C_{1-10} aliphatic chain. Particular examples include optionally substituted straight or branched chain C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl chains.

Heteroaliphatic chains represented by Alk^1 or Alk^2 include the aliphatic chains just described but with each chain additionally containing one, two, three or four heteroatoms or heteroatom-containing groups. Particular heteroatoms or groups include atoms or groups L^5 where L^5 is as defined above for L^1 when L^1 is a linker atom or group. Each L^5 atom or group may interrupt the aliphatic chain, or may be positioned at its terminal carbon atom to connect the chain to the atom or group R^1 or R^6.

Particular examples of aliphatic chains represented by Alk^1 or Alk^2 include optionally substituted $-CH_2-$, $-CH_2CH_2-$, $-(CH_2)_2CH_2-$, $-CH(CH_3)CH_2-$, $-(CH_2)_3CH_2-$, $-CH(CH_3)CH_2CH_2-$, $-CH_2CH(CH_3)CH_2-$, $-C(CH_3)_2CH_2-$, $-(CH_2)_4CH_2-$, $-(CH_2)_5CH_2-$, -CHCH-, $-CHCHCH_2-$, $-CH_2CHCH-$, $-CHCHCH_2CH_2-$, $-CH_2CHCHCH_2-$, $-(CH_2)_2CHCH-$, -CC-, $-CCCH_2-$, $-CH_2CC-$, $-CCCH_2CH_2-$, $-CH_2CCCH_2-$, or $-(CH_2)_2CC-$ chains. Where appropriate each of said chains may be optionally interrupted by one or two atoms and/or groups L^5 to form an optionally substituted heteroaliphatic chain. Particular examples include optionally substituted $-L^5CH_2-$, $-CH_2L^5CH_2-$, $-L^5(CH_2)_2-$, $-CH_2L^5(CH_2)_2-$, $-(CH_2)_2L^5CH_2-$, $-L^5(CH_2)_3-$ and $-(CH_2)_2L^5(CH_2)_2-$ chains.

When R^1 and/or R^6 is present in compounds of formula (1) as an optionally substituted cycloaliphatic group it may be an optionally substituted C_{3-10} cycloaliphatic group. Particular examples include optionally substituted C_{3-10}cycloalkyl, e.g. C_{3-7}cycloalkyl, C_{3-10}cycloalkenyl e.g. C_{3-7}cycloalkenyl or C_{3-10}cycloalkynyl e.g. C_{3-7}cycloalkynyl groups.

Optionally substituted heterocycloaliphatic groups represented by R^1 or R^6 include the optionally substituted cycloaliphatic groups just described for R^1 and R^6 but with each group additionally containing one, two, three or four heteroatoms or heteroatom-containing groups L^3 as just defined.

Optionally substituted polycycloaliphatic groups represented by R^1 and/or R^6 include optionally substitued C_{7-10} bi- or tricycloalkyl or C_{7-10}bi- or tricycloalkenyl groups. Optionally substituted polyheterocycloaliphatic groups represented by R^1 and/or R^6 include the optionally substituted polycycloalkyl groups just described, but with each group additionally containing one, two, three or four L^3 atoms or groups.

Particular examples of R^1 or R^6 cycloaliphatic, polycycloaliphatic, heterocycloaliphatic and polyheterocycloaliphatic groups include optionally substituted cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, 2-cyclobuten-1-yl, 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, 2,4-cyclopentadien-1-yl, 3,5,-cyclohexadien-1-yl, adamantyl, norbornyl,

norbornenyl, pyrroline, e.g. 2- or 3-pyrrolinyl, pyrrolidinyl, pyrrolidinone, oxazolidinyl, oxazolidinone, dioxolanyl, e.g. 1,3-dioxolanyl, imidazolinyl, e.g. 2-imidazolinyl, imidazolidinyl, pyrazolinyl, e.g. 2-pyrazolinyl, pyrazolidinyl, pyranyl, e.g. 2- or 4-pyranyl, piperidinyl, piperidinone, 1,4-dioxanyl, morpholinyl, morpholinone, 1,4-dithianyl, thiomorpholinyl, piperazinyl, 1,3,5-trithianyl, oxazinyl, e.g. 2H-1,3-, 6H-1,3-, 6H-1,2-, 2H-1,2- or 4H-1,4- oxazinyl, 1,2,5-oxathiazinyl, isoxazinyl, e.g. o- or p-isoxazinyl, oxathiazinyl, e.g. 1,2,5 or 1,2,6-oxathiazinyl, or 1,3,5,2-oxadiazinyl groups.

The optional substituents which may be present on the Alk^1, Alk^2, R^1 or R^6 aliphatic heteroaliphatic, cycloaliphatic, polycycloaliphatic or hetero-cycloaliphatic or polyheterocycloaliphatic groups include one, two, three or more substituents selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or hydroxyl, C_{1-6}alkoxy, e.g. methoxy or ethoxy, thiol, C_{1-6}alkylthio e.g. methylthio or ethylthio, amino or substituted amino groups. Substituted amino groups include $-NHR^{11}$ and $-N(R^{11})_2$ groups where R^{11} is as defined above.

In the compounds of formula (1), optionally substituted aromatic groups represented by the group R^1 and/or R^6 include for example optionally substituted monocyclic or bicyclic fused ring C_{6-12} aromatic groups, such as optionally substituted phenyl, 1- or 2-naphthyl, 1- or 2-tetrahydronaphthyl, indanyl or indenyl groups .

Optionally substituted aromatic groups represented by the group R^1 or R^6 in compounds of formula (1) include for example optionally substituted monocyclic or bicyclic fused ring C_{6-12} aromatic groups, such as optionally substituted phenyl, 1- or 2-naphthyl, 1- or 2-tetrahydronaphthyl, indanyl or indenyl groups .

Optionally substituted heteroaromatic groups, represented by the group R^1 or R^6 in compounds of formula (1) include for example optionally substituted C_{1-9} heteroaromatic groups containing for example one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. In general, the heteroaromatic groups may be for example

monocyclic or bicyclic fused ring heteroaromatic groups. Monocyclic heteroaromatic groups include for example five- or six-membered heteroaromatic groups containing one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. Bicyclic heteroaromatic groups include for example nine- to thirteen-membered fused-ring heteroaromatic groups containing one, two or more heteroatoms selected from oxygen, sulphur or nitrogen atoms.

Particular examples of heteroaromatic groups of these types include optionally substituted pyrrolyl, furyl, thienyl, imidazolyl, N-methylimidazolyl, N-ethylimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,3,4-thiadiazole, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, benzofuryl, [2,3-dihydro]benzofuryl, isobenzofuryl, benzothienyl, benzoriazolyl, isobenzothienyl, indolyl, isoindolyl, benzimidazolyl, imidazo[1,2-a]pyridyl, benzothiazolyl, benzoxazolyl, benzopyranyl, [3,4-dihydro]benzopyranyl, quinazolinyl, naphthyridinyl, pyrido[3,4-b]pyridyl, pyrido[3,2-b]pyridyl, pyrido[4,3-b]pyridyl, quinolinyl, isoquinolinyl, tetrazolyl, 5,6,7,8-tetrahydroquinolinyl, 5,6,7,8-tetrahydroisoquinolinyl, and imidyl, e.g. succinimidyl, phthalimidyl, or naphthalimidyl such as 1,8-naphthalimidyl.

Optional substituents which may be present on aromatic or heteroaromatic groups of the above types include one, two, three or more substituents selected from the group $-L^3(CH_2)_pL^4(R^{2a})_q$ where L^3, L^4, p and q are as defined previously and R^{2a} is as previously defined but is other than an hydrogen atom when L^3 and L^4 is each a covalent bond and p is zero.

Examples of the substituents represented by R^2 and R^3 in compounds of formula (1) and which may be present on aromatic or heteroaromatic groups represented by R^1 and R^6 include atoms or groups $-L^3(CH_2)_pL^4R^{2a}$, $-L^3(CH_2)_pR^{2a}$, $-L^3R^{2a}$, $-(CH_2)_pR^{2a}$ and $-R^{2a}$ wherein L^3, $(CH_2)_p$, L^4 and R^{2a} are as defined above. Particular examples of such substituents include $-L^3CH_2L^3R^{2a}$, $-L^3CH(CH_3)L^4R^{2a}$, $-L^3CH(CH_2)_2L^4R^{2a}$, $-L^3CH_2R^{2a}$, $-L^3CH(CH_3)R^{2a}$, $-L^3(CH_2)_2R^{2a}$, $-CH_2R^{2a}$, $-CH(CH_3)R^{2a}$ and $-(CH_2)_2R^{2a}$ groups.

Thus each of R^2 and R^3 and, where present, substituents on R^1 and R^6 aromatic or heteroaromatic groups in compounds of the invention may be for example selected from a hydrogen atom, a halogen atom, e.g. a fluorine, chlorine, bromine or iodine atom, or a C_{1-6}alkyl, e.g. methyl, ethyl, n-propyl, i-propyl, n-butyl or t-butyl, C_{1-6}alkylamino, e.g. methylamino or ethylamino, C_{1-6}hydroxyalkyl, e.g. hydroxymethyl, hydroxyethyl or $-C(OH)(CF_3)_2$, carboxyC_{1-6}alkyl, e.g. carboxyethyl, C_{1-6}alkylthio e.g. methylthio or ethylthio, carboxyC_{1-6}alkylthio, e.g. carboxymethylthio, 2-carboxyethylthio or 3-carboxypropylthio, C_{1-6}alkoxy, e.g. methoxy or ethoxy, hydroxyC_{1-6}alkoxy, e.g. 2-hydroxyethoxy, haloC_{1-6}alkyl, e.g. $-CF_3$, CCl_3, $-CHF_2$, $-CHCl_2$, $-CH_2F$, $-CH_2Cl$, haloC_{1-6}alkoxy, e.g. $-OCF_3$, $-OCCl_3$, $-OCHF_2$, $-OCHCl_2$, $-OCH_2F$, $-OCH_2Cl$, C_{1-6}alkyl-amino, e.g. methylamino or ethylamino, amino ($-NH_2$), aminoC_{1-6}alkyl, e.g. aminomethyl or aminoethyl, C_{1-6}dialkylamino, e.g. dimethylamino or diethylamino, C_{1-6} alkylaminoC_{1-6}alkyl, e.g. ethylaminoethyl, C_{1-6}dialkyl-aminoC_{1-6}alkyl, e.g. diethylaminoethyl, aminoC_{1-6}alkoxy, e.g. aminoethoxy, C_{1-6}alkylaminoC_{1-6}alkoxy, e.g. methylaminoethoxy, C_{1-6}dialkylaminoC_{1-6}alkoxy, e.g. dimethylaminoethoxy, diethylaminoethoxy, isopropylaminoethoxy, or dimethylaminopropoxy, nitro, cyano, amidino, hydroxyl (-OH), formyl [HC(O)-], carboxyl ($-CO_2H$), $-CO_2R^{12}$, C_{1-6} alkanoyl e.g. acetyl, thiol (-SH), thioC_{1-6}alkyl, e.g. thiomethyl or thioethyl, sulphonyl ($-SO_3H$), C_{1-6}alkylsulphonyl, e.g. methylsulphonyl, aminosulphonyl ($-SO_2NH_2$), C_{1-6}alkylaminosulphonyl, e.g. methylaminosulphonyl or ethylamino-sulphonyl, C_{1-6}dialkylaminosulphonyl, e.g. dimethylaminosulphonyl or diethylaminosulphonyl, phenylaminosulphonyl, carboxamido ($-CONH_2$), C_{1-6}alkylaminocarbonyl, e.g. methylaminocarbonyl or ethylaminocarbonyl, C_{1-6}dialkylaminocarbonyl, e.g. dimethylaminocarbonyl or diethylamino-carbonyl, aminoC_{1-6}alkylaminocarbonyl, e.g. aminoethylaminocarbonyl, C_{1-6}dialkylaminoC_{1-6}alkylaminocarbonyl, e.g. diethylaminoethylamino-carbonyl, aminocarbonylamino, C_{1-6}alkylaminocarbonylamino, e.g. methylaminocarbonylamino or ethylaminocarbonylamino, C_{1-6}dialkyl-aminocarbonylamino, e.g. dimethylaminocarbonylamino or diethylamino-carbonylamino, C_{1-6}alkylaminocabonylC_{1-6}alkylamino, e.g. methylamino-carbonylmethylamino, aminothiocarbonylamino, C_{1-6}alkylaminothio-carbonylamino, e.g. methylaminothiocarbonylamino or ethylaminothio-

carbonylamino, C_{1-6}dialkylaminothiocarbonylamino, e.g. dimethylaminothiocarbonylamino or diethylaminothiocarbonylamino, C_{1-6}alkylaminothiocarbonylC_{1-6}alkylamino, e.g. ethylaminothiocarbonylmethylamino, C_{1-6}alkylsulphonylamino, e.g. methylsulphonylamino or ethylsulphonylamino, C_{1-6}dialkylsulphonylamino, e.g. dimethylsulphonylamino or diethylsulphonylamino, aminosulphonylamino ($-NHSO_2NH_2$), C_{1-6}alkylaminosulphonylamino, e.g. methylaminosulphonylamino or ethylaminosulphonylamino, C_{1-6}dialkylaminosulphonylamino, e.g. dimethylaminosulphonylamino or diethylaminosulphonylamino, C_{1-6}alkanoylamino, e.g. acetylamino, aminoC_{1-6}alkanoylamino e.g. aminoacetylamino, C_{1-6}dialkylaminoC_{1-6}alkanoylamino, e.g. dimethylaminoacetylamino, C_{1-6}alkanoylaminoC_{1-6}alkyl, e.g. acetylaminomethyl, C_{1-6}alkanoylaminoC_{1-6}alkylamino, e.g. acetamidoethylamino, C_{1-6}alkoxycarbonylamino, e.g. methoxycarbonylamino, ethoxycarbonylamino or t-butoxycarbonylamino group.

In one group of compounds of the invention R^2 and R^3 may each be a hydrogen or halogen atom or a straight or branched alkyl, haloalkyl, alkoxy, haloalkoxy, hydroxyl or nitro group as defined herein.

The chain represented by A in compounds of the invention may for example be a chain $-Y[C(R^9)(R^{10})]_2-$, $-[C(R^7)(R^8)]Y[C(R^9)(R^{10})]-$, $-[C(R^7)(R^8)]_2Y-$, $-[C(R^7)(R^8)]_2Y[(R^9)(R^{10})]-$ or $-[C(R)^7(R)^8]Y[C(R^9)(R^{10})]_2-$ where Y, R^7, R^8, R^9 and R^{10} are as described above for compounds of formula (1). Particular examples of such chains include $-Y(CH_2)_2-$, $-(CH_2)_2Y-$, $-CH_2YCH_2-$, $-[C(R^7)(R^8)]YCH_2-$ e.g. $-C(CH_3)_2YCH_2-$ and $-CH_2Y[C(R^9)(R^{10})]-$ e.g. $-CH_2YC(CH_3)_2-$ chains.

When in the chain represented by A, R^7, R^8, R^9 and/or R^{10} is an optionally substituted aromatic group it may be an optionally substituted phenyl group. Particular examples of optional substituents include one, two or three substituents selected from halogen atoms, e.g. fluorine, bromine, chlorine or iodine atoms or C_{1-6}alkyl, e.g. methyl or ethyl, C_{1-6}alkoxy, e.g. methoxy or ethoxy, hydroxy, nitro or cyano groups. When one of R^7, R^8, R^9 or R^{10} is an optionally substituted aromatic group, the remainder for

example may each be a hydrogen atom or a straight or branched alkyl group as defined herein.

The presence of certain substituents in the compounds of formula (1) may enable salts of the compounds to be formed. Suitable salts include pharmaceutically acceptable salts, for example acid addition salts derived from inorganic or organic acids, and salts derived from inorganic and organic bases.

Acid addition salts include hydrochlorides, hydrobromides, hydroiodides, alkylsulphonates, e.g. methanesulphonates, ethanesulphonates, or isethionates, arylsulphonates, e.g. p-toluenesulphonates, besylates or napsylates, phosphates, sulphates, hydrogen sulphates, acetates, trifluoroacetates, propionates, citrates, maleates, fumarates, malonates, succinates, lactates, oxalates, tartrates and benzoates.

Salts derived from inorganic or organic bases include alkali metal salts such as sodium or potassium salts, alkaline earth metal salts such as magnesium or calcium salts, and organic amine salts such as morpholine, piperidine, dimethylamine or diethylamine salts.

Particularly useful salts of compounds according to the invention include pharmaceutically acceptable salts, especially acid addition pharmaceutically acceptable salts.

R in compounds of the invention is preferably a $-CO_2H$ group.

Alk^3 in compounds of formula (1) is preferably a $-CH_2-$ chain and m is preferably an integer 1. In compounds of this type, the carbon atom to which Alk^3 and R are attached forms a chiral centre and is preferably in the L configuration.

R^4 and R^5 in compounds of the invention is each preferably a hydrogen atom.

One particular class of compounds of the invention is that wherein each of R^7, R^8, R^9 and R^{10} in the chain A is as defined for formula (1) other than an optionally substituted aromatic group. In general in compounds of formula (1) the chain A is one in which Y is preferably a sulphur atom. Particularly useful chains represented by A include $-C(R^7)(R^8)SC(R^9)(R^{10})-$ chains, especially $-CH_2SCH_2-$, $-CH(CH_3)SCH_2-$, $-C(CH_3)_2SCH_2-$, $-CH_2SCH(CH_3)-$ and $-CH_2SC(CH_3)_2-$ chains. Compounds of the invention in which A is $-CH_2SCH_2-$ are particularly preferred.

When the linker group L^1 is present in compounds of the invention [i.e. when s is an integer 1] it is preferably an oxygen atom or a -C(O)O-, -C(O)NH-, $-C(O)N(CH_3)-$, -C(S)NH-, -NH-, $-N(CH_3)-$, -NHC(O)O-, $-SO_2-$, $-SO_2NH-$, $-SO_2N(CH_3)-$, -OC(O)NH-, -NHC(O)NH- or -NHC(S)NH- group. Especially useful L^1 groups include $-SO_2NH-$, -C(O)O-, -NH- and, in particular, -CONH-.

The aliphatic chain represented by Alk^1 in compounds of formula (1) is preferably a $-CH_2-$ chain.

In general in compounds of the invention the group R^1 is preferably an optionally substituted aromatic or heteroaromatic group. Particularly useful groups of these types include optionally substituted six-membered monocyclic groups, especially optionally substitued phenyl, pyridyl or pyrimidinyl groups.

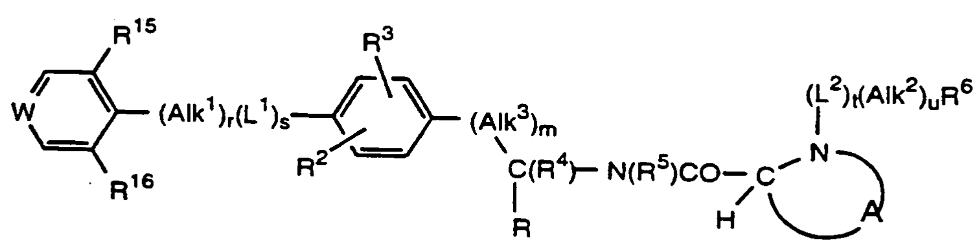
Compounds of the invention in which a linker group L^2 is present (i.e. when t is an integer 1) are preferred. Compounds of this type in which L^2 is a -C(O)- group are particularly useful.

Alk^2 in compounds of formula (1) is preferably present (i.e. u is preferably an integer 1) and in particular is a $-CH_2-$ chain. Compounds of this type in which R^6 is a hydrogen atom or an optionally substituted aromatic or heteroaromatic group, especially an optionally substituted phenyl, pyridyl or imidazolyl group are particularly preferred.

A particularly useful class of compounds according to the invention has the formula (1) in which $R^1(Alk^1)_r(L^1)_s$- is a $R^1CH_2L^1$ or R^1L^1 group where R^1 is an optionally substituted aromatic or heteroaromatic group and L^1 is a linker atom or group, Alk^3 is a $-CH_2-$ chain, m is an integer 1, R^4 is a hydrogen atom, R^5 is a hydrogen atom and $-(L^2)_t(Alk^2)_uR^6$ is preferably a $-L^2CH_2R^6$ group where R^6 is a hydrogen atom or an optionally substituted aromatic or heteroaromatic group and is especially a $-C(O)CH_2R^6$ group where R^6 is as just defined. A particular group of compounds in this class include compounds in which R^6 is an optionally substituted heteroaromatic group, particularly an optionally substituted pyridyl group. In general in compounds in this class $R^1CH_2L^1$ is preferably a R^1CH_2S, $R^1CH_2S(O)$-, $R^1CH_2S(O)_2$, $R^1CH_2C(O)$, $R^1CH_2N(R^{11})$- or, especially, a R^1CH_2O- group; and R^1L^1 is preferably a $R^1CSN(R^{11})$-, $R^1N(R^{11})CO$-, $R^1N(R^{11})CS$-, $R^1S(O)N(R^{11})$-, $R^1S(O)_2N(R^{11})$-, $R^1N(R^{11})SO$-, $R^1N(R^{11})S(O)_2$- or, especially, a $R^1CON(R^{11})$- group, particularly a R^1CONH- group.

In the compounds of the just mentioned class R is especially a $-CO_2H$ group.

An especially useful group of compounds according to the invention has the formula (1a):



(1a)

wherein -W= is -CH= or -N=; R^{15} and R^{16},which may be the same or different, is each an atom or group $-L^3(CH_2)_pL^4(R^{2a})_q$ as defined for R^2 and R^3 in formula (1): Alk^1,r, L^1,s, R^2, R^3, Alk^3, m, R, R^4, R^5, A, L^2, t, Alk^2, u and R^6 are as defined generally and particularly for formula (1); and the salts, solvates, hydrates and N-oxides thereof.

It will be appreciated that the various preferences stated above in relation to groups present in compounds of formula (1) apply equally to the same groups when present in compounds of formula (1a).

Additionally, in the compounds of formula (1a) the group $(Alk^1)_r(L^1)_s$ is preferably a $-SO_2NH-$, -C(O)O-, -NH- or, especially a -CONH- group.

One of R^{15} or R^{16} in compounds of formula (1a) may be a hydrogen atom and the other a substituent $-L^3(CH_2)_pL^4(R^{2a})_q$ in which R^{2a} is not a hydrogen atom when L^3 and L^4 is each a covalent bond and p is zero, but preferably each of R^{15} and R^{16} is a substituent $-L^3(CH_2)_pL^4(R^{2a})_q$ as just defined. Particularly useful R^{15} or R^{16} substituents include halogen atoms, especially fluorine or chlorine atoms, methyl, ethyl, methoxy, ethoxy, $-CF_3$, -OH, -CN, $-NO_2$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-COCH_3$, $-SCH_3$, $-CO_2H$ or $-CO_2CH_3$ groups.

-W= in compounds of formula (1a) is preferably -N=.

Particularly useful compounds according to the invention include the following:

N-(Pyrid-3-ylacetyl)-*D*-thioproline-(*N'*-2,6-dichlorobenzoyl)-*L*-4-aminophenylalanine;
N-Acetyl-*D*-thioproline-(*N'*-3,5-dichloroisonicotinoyl)-*L*-4-amino phenylalanine;
N-(Pyrid-3-ylacetyl)-*D*-thioproline-*O*-(2,4,6-trichlorobenzyl)-*L*-tyrosine;
N-(Pyrid-3-ylacetyl)-*D*-thioproline-(*O*-2,4,6-trichlorobenzoyl)-*L*-tyrosine;
N-(Pyrid-3-ylacetyl)-*D*-thioproline-(*O*-2,6-dichlorobenzoyl)-*L*-tyrosine;
N-Acetyl-*D*-thioproline-(*N'*-2,6-dichlorobenzoyl)-*L*-4-aminophenylalanine;
N-Acetyl-*D*-thioproline-[*N'*-2-fluoro-6-(trifluoromethyl)benzoyl]-*L*-4-aminophenylalanine;
N-Acetyl-*D*-thioproline-(*N'*-2,4,6-trichlorobenzoyl)-*L*-4-aminophenylalanine;
N-Acetyl-*D*-thioproline-(*N'*-2,6-trichlorobenzyl)-*L*-4-aminophenylalanine;
and the salts, solvates, hydrates and N-oxides thereof.

It will be appreciated that where appropriate the provisos applying to compounds of general formula (1) apply equally to the above-mentioned specific classes of compounds of formula (1).

Compounds according to the invention are potent and selective inhibitors of $\alpha4$ integrins. The ability of the compounds to act in this way may be simply determined by employing tests such as those described in the Examples hereinafter.

The compounds are of use in modulating cell adhesion and in particular are of use in the prophylaxis and treatment of diseases or disorders involving inflammation in which tyhe extravasation of leukocytes plays a role. Diseases or disorders of this type include inflammatory arthritis such as rheumatoid arthritis vasculitis or polydermatomyositis, multiple sclerosis, allograft rejection, diabetes, inflammatory dermatoses such as psoriasis or dermatitis, asthma and inflammatory bowel disease.

For the prophylaxis or treatment of disease the compounds according to the invention may be administered as pharmaceutical compositions, and according to a further aspect of the invention we provide a pharmaceutical composition which comprises a compound of formula (1) together with one or more pharmaceutically acceptable carriers, excipients or diluents.

Pharmaceutical compositions according to the invention may take a form suitable for oral, buccal, parenteral, nasal, topical or rectal administration, or a form suitable for administration by inhalation or insufflation.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets, lozenges or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for

oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents, emulsifying agents, non-aqueous vehicles and preservatives. The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds for formula (1) may be formulated for parenteral administration by injection e.g. by bolus injection or infusion. Formulations for injection may be presented in unit dosage form, e.g. in glass ampoule or multi dose containers, e.g. glass vials. The compositions for injection may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising, preserving and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

In addition to the formulations described above, the compounds of formula (1) may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation or by intramuscular injection.

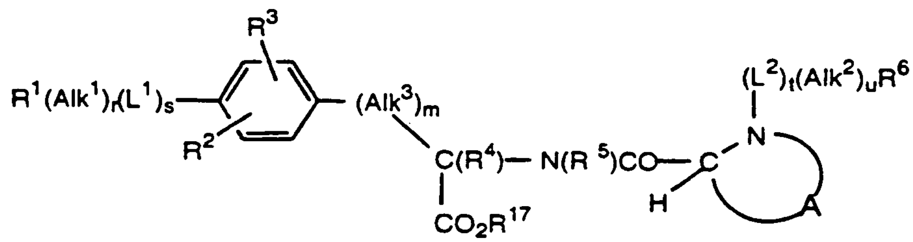
For nasal administration or administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation for pressurised packs or a nebuliser, with the use of suitable propellant, e.g. dichlorodifluoromethane, trichloro-fluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas or mixture of gases.

The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack or dispensing device may be accompanied by instructions for administration.

The quantity of a compound of the invention required for the prophylaxis or treatment of a particular condition will vary depending on the compound chosen, and the condition of the patient to be treated. In general, however, daily dosages may range from around 100ng/kg to 100mg/kg e.g. around 0.01mg/kg to 40mg/kg body weight for oral or buccal administration, from around 10ng/kg to 50mg/kg body weight for parenteral administration and around 0.05mg to around 1000mg e.g. around 0.5mg to around 1000mg for nasal administration or administration by inhalation or insufflation.

The compounds of the invention may be prepared by a number of processes as generally described below and more specifically in the Examples hereinafter. In the following process description, the symbols R^1-R^6, L^1, L^2, Alk^1, Alk^2, Alk^3, m, r, s, t, u and A when used in the formulae depicted are to be understood tc represent those groups described above in relation to formula (1) unless otherwise indicated. In the reactions described below, it may be necessary to protect reactive functional groups, for example hydroxy, amino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice [see, for example, Green, T. W. in "Protective Groups in Organic Synthesis", John Wiley and Sons, 1991]. In some instances, deprotection may be the final step in the synthesis of a compound of formula (1) and the processes according to the invention described hereinafter are to be understood to extend to such removal of protecting groups.

Thus according to a further aspect of the invention, a compound of formula (1) may be obtained by hydrolysis of an ester of formula (2):

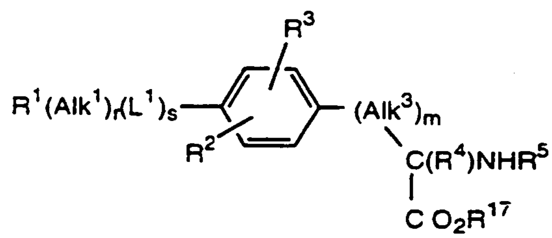


(2)

where R^{17} is an alkyl group.

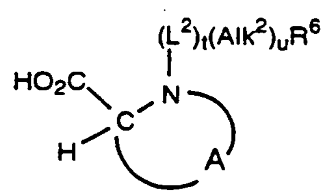
The hydrolysis may be performed using either an acid or a base depending on the nature of R^{12}, for example an organic acid such as trifluoroacetic acid or an inorganic base such as lithium hydroxide or potassium carbonate optionally in an aqueous organic solvent such as an amide, e.g. a substituted amide such as dimethylformamide, an ether, e.g. a cyclic ether such as tetrahydrofuran or dioxane or an alcohol, e.g. methanol at around ambient temperature. Where desired, mixtures of such solvents may be used.

Esters of formula (2) may be prepared by coupling an amine of formula (3):



(3)

(where R^{12} is as just described) or a salt thereof with an acid of formula (4):



(4)

or an active derivative thereof.

Active derivatives of acids of formula (4) include anhydrides, esters and halides. Particular esters include pentafluorophenyl or succinyl esters.

The coupling reaction may be performed using standard conditions for reactions of this type. Thus for example the reaction may be carried out in a solvent, for example an inert organic solvent such as an amide, e.g. a substituted amide such as dimethylformamide, an ether, e.g. a cyclic ether such as tetrahydrofuran, or a halogenated hydrocarbon, such as dichloromethane, at a low temperature, e.g. around -30°C to around ambient temperature, optionally in the presence of a base, e.g. an organic base such as an amine, e.g. triethylamine, pyridine, or dimethylaminopyridine, or a cyclic amine, such as N-methylmorpholine.

Where an acid of formula (4) is used, the reaction may additionally be performed in the presence of a condensing agent, for example a diimide such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide or N,N'-dicyclohexylcarbodiimide, advantageously in the presence of a catalyst such as a N-hydroxy compound e.g. a N-hydroxytriazole such as 1-hydroxybenzotriazole. Alternatively, the acid may be reacted with a chloroformate, for example ethylchloroformate, prior to reaction with the amine of formula (3).

Where appropriate the coupling reaction may be carried out earlier in the synthesis of the compound of the invention, for example by using an acid of formula (4) where $R^6(Alk^2)_u(L^2)_t$- is a hydrogen atom and manipulating the resulting ester to introduce any desired $R(^6Alk^2)_u(L^2)_t$- group. Similarly, intermediate esters of formula (2), or compounds of formula (1), may be manipulated to introduce particular $R^6(Alk^2)_r(L^1)_s$-, R^2 and/or R^3 groups or modify existing R^1 and/or R^6 substituents. Typically, such manipulation may involve standard substitution approaches employing for example alkylation, arylation, acylation, halogenation, sulphonylation, nitration or coupling reactions.

Thus in one example, a compound wherein $R^1(Alk^1)_r(L^1)_s$- is a -L^1H group may be alkylated or arylated using a reagent $R^1(Alk^1)_rX$ in which R^1 is

other than a hydrogen atom and X is a leaving atom or group such as a halogen atom, e.g. a fluorine, bromine, iodine or chlorine atom or a sulphonyloxy group such as an alkylsulphonyloxy, e.g. trifluoromethylsulphonyloxy or arylsulphonyloxy, e.g. p-toluenesulphonyloxy group.

The alkylation or arylation reaction may be carried out in the presence of a base such as a carbonate, e.g. caesium or potassium carbonate, an alkoxide, e.g. potassium t-butoxide, or a hydride, e.g. sodium hydride, in a dipolar aprotic solvent such as an amide, e.g. a substituted amide such as dimethylformamide or an ether, e.g. a cyclic ether such as tetrahydrofuran.

In another example, a compound where $R^1(Alk^1)_r(L^1)_s$ is a $-L^1H$ group and/or $R^6(Alk^2)_2(L^2)_2$- is a hydrogen atom may be functionalised by acylation, for example by reaction with a reagent $R^1(Alk^1)_rL^1X$ [wherein L^1 is a -C(O)-, $-CH_2C(O)-$ or -NHC(O)- group], $R^6(Alk^2)_uCOX$ or $R^6(Alk^2)_uNHCOX$ in the presence of a base, such as a hydride, e.g. sodium hydride or an amine, e.g. triethylamine or N-methylmorpholine, in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane or carbon tetrachloride or an amide, e.g. dimethylformamide, at for example ambient temperature, or by reaction with $R^1(Alk^1)_rCO_2H$ or $R^6(Alk^2)_uCO_2H$ or an activated derivative thereof, for example as described above for the preparation of esters of formula (2).

In a further example a compound may be obtained by sulphonylation of a compound where $R^1(Alk^1)_r(L^1)_s$ is an -OH group by reaction with a reagent $R^1(Alk^1)_rL^1Hal$ [in which L^1 is $-SO_2-$ and Hal is a halogen atom such as a chlorine atom] in the presence of a base, for example an inorganic base such as sodium hydride in a solvent such as an amide, e.g. a substituted amide such as dimethylformamide at for example ambient temperature.

In another example, a compound where $R^1(Alk^1)_r(L^1)_s$ is a $-L^1H$ group, may be coupled with a reagent R^1OH (where R^1 is other than a hydrogen atom) or R^1Alk^1OH in a solvent such as tetrahydrofuran in the presence of a phosphine, e.g. triphenylphosphine and an activator such as diethyl,

diisopropyl- or dimethylazodicarboxylate to yield a compound containing a $R^1(Alk^1)_rO$- group.

Intermediates of formulae (3) and (4), $R^1(Alk^1)_rX$, $R^1((Alk^1)_rL^1X$, $R^6(Alk^2)_uCOX$, $R^6(Alk^2)_uNHCOX$, $R^1(Alk^1)_rCO_2H$, $R^6(Alk^2)_uCO_2H$, R^1OH and R^1Alk^1OH are either known compounds or may be prepared from known starting materials by use of analogous processes to those used for the preparation of the known compounds and/or by treating known compounds using standard substitution approaches, for example by one or more of the alkylation, acylation, arylation, sulphonylation, hydrogenation and other manipulations described herein, such as particularly described for the preparation of the Intermediates in the exemplification section hereinafter.

Salts of compounds of formula (1) may be prepared by reaction of a compound of formula (1) with an appropriate base in a suit able solvent or mixture of solvents e.g. an organic solvent such as an ether e.g. diethylether, or an alcohol, e.g. ethanol using conventional procedures.

Where it is desired to obtain a particular enantiomer of a compound of formula (1) this may be produced from a corresponding mixture of enantiomers using any suitable conventional procedure for resolving enantiomers.

Thus for example diastereomeric derivatives, e.g. salts, may be produced by reaction of a mixture of enantiomers of formula (1) e.g. a racemate, and an appropriate chiral compound, e.g. a chiral base. The diastereomers may then be separated by any convenient means, for example by crystallisation and the desired enantiomer recovered, e.g. by treatment with an acid in the instance where the diastereomer is a salt.

In another resolution process a racemate of formula (1) may be separated using chiral High Performance Liquid Chromatography. Alternatively, if desired a particular enantiomer may be obtained by using an appropriate chiral intermediate in one of the processes described above.

The following Examples illustrate the invention. All temperatures are in °C. The following abbreviations are used:

EDC - 1-(3-dimethylaminopropyl)3-ethycarbodiimide;

DMF - dimethylformamide;	DMSO - dimethylsulphoxide;
HOBT - 1-hydroxybenzotriazole;	THF - tetrahydrofuran;
TFA - trifluoroacetic acid;	NMM - N-methylmorpholine;
DCM - dichloromethane;	Ph - phenyl;
Boc - tert-butoxycarbonyl;	EtOAc - ethyl acetate;
MeOH - methanol;	LDA - lithium diisopropylamide
tyr - tyrosine;	Ar - aryl;
HetAr - heteroaryl;	pyr - pyridine;
thiopro - thioproline;	Bu - butyl
app. - apparent;	AcOH - acetic acid;
Et_2O - diethylether;	sym. - symmetrical;
EtOH - ethanol	

DBU - 1,8-diazabicyclo[5.4.0]undec-7-ene

INTERMEDIATE 1

***N*-Boc-*D*-thioproline-*L*-4-aminophenylalanine methyl ester**

EDC (11.31g, 59mmol) was added over a period of 5mins to an ice cold solution of 4-aminophenylalanine methyl ester dihydrochloride (14.3g, 54mmol), HOBT (8.67g, 64mmol), NMM (16.2g, 17.6ml, 160mmol) and *N*-Boc-*D*-thioproline (13.74g, 59mmol) in DMF (150ml). The reaction was warmed to room temperature and stirred for 16h. The volatiles were evaporated *in vacuo* and the residue partitioned between EtOAc (200ml) and saturated Na_2CO_3 solution (100ml). The organic layer was separated, washed with saturated Na_2CO_3 (2x100ml) and brine (50ml), dried over $MgSO_4$ and the solvent evaporated *in vacuo*. The product was purified by chromatography (SiO_2; DCM MeOH 97:3) to give the title compound as a pale orange foam (15g, 64%). δH (DMSO-d^6, 360K) 7.87 (1H, d, *J* 8.0Hz, NH), 6.84 (2H, d, *J* 8.3Hz, Ar-H), 6.50 (2H, d, *J* 8.3Hz, Ar-H), 4.62 (1H, d, *J* 9.1Hz, $NC\underline{H}_AH_BS$), 4.60 (1H, m, CH_α-thiopro), 4.48 (1H, dt, *J* 5.8, 8.2Hz, $CH_\alpha Ph$), 4.27 (1H, d, *J* 9.1Hz, $NCH_A\underline{H}_BS$), 3.62 (3H, s, CO_2CH_3), 3.23 (1H, dd, *J* 7.5, 11.6Hz, $CHC\underline{H}_AH_BS$), 2.91-2.75 (3H, m, $CHCH_AC\underline{H}_BS$ and CH_2Ar) and 1.40 (9H, s, ^tBu). m/z (ESI, 15V) 410 (MH^+).

INTERMEDIATE 2

***N*-Boc-*D*-thioproline-(*N'*-2,6-dichlorobenzoyl)-*L*-4-aminophenylalanine methyl ester**

2,6-Dichlorobenzoyl chloride (0.61g, 2.9mmol) was added to a solution of Intermediate 1 (1.0g, 2.4mmol) and NMM (0.28g, 2.88mmol) in DCM (10ml). The reaction was stirred at room temperature for 16h then partitioned between DCM (50ml) and saturated Na_2CO_3 solution (20ml). The aqueous layer was separated and extracted with DCM (2x50ml). The combined organic layers were washed with brine (50ml), dried over $MgSO_4$ and the solvent evaporated *in vacuo* to give a foam which was purified by chromatography (SiO_2; DCM/MeOH 97:3) to give the title compound as a white foam (1.3g, 91%). δH (DMSO-d^6, 350K) 10.41 (1H, s, NH), 8.08 (1H, d, *J* 8.2Hz, NH), 7.59 (2H, d, *J* 8.5Hz, Ar-H), 7.55 -7.44 (3H, m, Ar-H), 7.19 (2H, d, *J* 8.5Hz, Ar-H), 4.62-4.56 (2H, m, CH_α-thiopro and CH_α-Ph), 4.62 (1H, d, *J* 9.1Hz, $NC\underline{H}_AH_BS$), 4.27 (1H, d, *J* 9.1Hz, $NCH_A\underline{H}_BS$), 3.66 (3H, s, CO_2CH_3), 3.23 (1H, dd, *J* 11.5, 7.5Hz, $CHC\underline{H}_AH_BS$), 2.91-2.75 (3H, m, $CHCH_A\underline{H}_BS$ and CH_2Ar) and 1.39 (9H, s, ^tBu). m/z (ESI, 15V) 582 (MH^+).

INTERMEDIATE 3

***D*-Thioproline-(*N'*-2,6-dichlorobenzoyl)-*L*-4-aminophenylalanine methyl ester hydrochloride**

A solution of Intermediate 2 (1.3g, 2.2mmol) in EtOAc (20ml) was treated with a solution of anhydrous EtOAc/hydrochloric acid (~4M, 10ml) and stood for 2.5h at room temperature. The volatiles were evaporated *in vacuo* to give the title compound as an off-white solid (1.2g, 98%). δH (CD_3OD) 8.86 (1H, d, *J* 8.6Hz, NH), 7.61 (2H, d, *J* 8.6Hz, Ar-H), 7.50-7.39 (3H, m, Ar-H), 7.23 (2H, d, *J* 8.6Hz, Ar-H), 4.87 (1H, m, CH_α-thiopro), 4.49 (1H, t, *J* 7.4Hz, CH_α-Ph), 4.35 (2H, s, NCH_2S), 3.64 (3H, s, CO_2CH_3), 3.42-3.27 (2H, m, $CHC\underline{H}_AH_BS$ and $ArC\underline{H}_AH_B$), and 3.00-2.73 (2H, m, $CHCH_A\underline{H}_BS$ and $ArCH_A\underline{H}_B$). m/z (ESI, 15V), 482, 484 (MH^+)

INTERMEDIATE 4

***N*-(Pyrid-3-ylacetyl)-*D*-thioproline-(*N'*-2,6-dichlorobenzoyl)-*L*-4-aminophenylalanine methyl ester**

EDC (0.48g, 2.5mmol) was added to a solution of Intermediate 3 (1.2g, 2.3mmol), HOBT (0.38g, 2.8mmol) NMM (0.51g, 5.1mmol) and 3-pyridylacetic acid hydrochloride (0.40g, 2.3mmol) in DMF (10ml) and the reaction stirred at room temperature for 16h. The volatiles were evaporated *in vacuo* and the residue partitioned between saturated Na_2CO_3 solution (30ml) and EtOAc (50ml). The organic layer was separated, washed with saturated Na_2CO_3 solution (30ml) and brine (30ml) and dried over $MgSO_4$. The solvent was evaporated *in vacuo* and the residue was purified by chromatography (SiO_2; DCM/MeOH 95:5) to give the title compound as a white foam (1.06g, 76%). δH (DMSO-d^6, 390K) 10.20 (1H, s, NH), 8.44 (2H, m, Ar-H), 7.63-7.17 (9H, m, pyr-H, Ar-H), 4.93 (1H, dd, *J* 4.0, 7.4Hz, CH_α-thiopro), 4.87 (1H, d, *J* 9.2Hz, $NC\underline{H}_AH_BS$), 4.61 (1H, dt, *J* 5.7, 8.2Hz, CH_α-Ph), 4.46 (1H, d, *J* 9.2Hz, $NCH_A\underline{H}_BS$), 3.74 (2H, m, CH_2pyr), 3.66 (3H, s, CO_2CH_3) and 3.32-2.95 (4H, m, $CHC\underline{H}_2S$ and Ar-$C\underline{H}_2$). *m/z* (ESI, 15V), 601 (MH^+).

INTERMEDIATE 5

***N*-Acetyl-*D*-thioproline-*L*-4-aminophenylalanine methyl ester**

NMM (1.13g, 1.24ml, 11.19mmol), HOBT (0.61g, 4.52mmol), N-acetyl-D-thioproline (0.72g, 4.11mmol) and EDC (0.79g, 4.11mmol) were added sequentially to a stirred solution of L-4-aminophenylalanine methyl ester dihydrochloride (1.0g, 3.75mmol) in dry DMF (10ml). After stirring at room temperature for 4h the solvent was removed *in vacuo*. The residue was partitioned between EtOAc (70ml) and 10% aqueous Na_2CO_3 (30ml). The phases were separated and the aqueous phase repeatedly extracted with EtOAc (4x30ml). The combined organic extracts were washed with brine (10ml), dried (Na_2SO_4) and evaporated *in vacuo*. The resulting oil was chromatographed (SiO_2; 3:97 to 5:95 MeOH/DCM) affording the title compound as a white foamy solid (0.97g, 74%): δH (CD_3OD) (two rotameric species) 6.93 (d, *J* 8.3Hz), and 6.91 (d, *J* 8.3Hz) together (2H, Ar$\underline{H}$), 6.64 (2H, d, *J* 8.3Hz, Ar$\underline{H}$), 4.81-4.60 (3H, m, $C\underline{H}\alpha$-thiopro, $C\underline{H}\alpha$-Ph, $NC\underline{H}_AH_BS$), 4.53 (d, *J* 10Hz), and 4.43 (d, *J* 10Hz) together (1H, $NCH_A\underline{H}_BS$), 3.71 (s) and 3.69 (s) together (3H, CO_2CH_3), 3.37-2.81 (4H,

m, $CHC\underline{H}_2S$ and $C\underline{H}_2Ar$), 2.14 (s) and 1.90 (s) together (3H, $COC\underline{H}_3$); m/z (ESI, 27V) 352 (MH^+).

INTERMEDIATE 6

3,5-Dichloro-isonicotinic acid

A solution of 3,5-dichloropyridine (5.00g, 33.8mmol) in THF (25ml) was added to a solution of LDA [generated from nBuLi (2.5M solution in hexanes, 14.9ml, 37.2mmol) and diisopropylamine (4.10g, 5.7ml, 40.6mmol)] in THF (25ml) at -78° under nitrogen, to give a yellow/brown slurry. The reaction was stirred for 30min at -78° then CO_2 gas was bubbled through to give a clear brown solution that slowly gave a precipitate, warmed to room temperature over 2h, then quenched with water (20ml) and partitioned between diethylether (100ml) and 1M NaOH (100ml). The aqueous layer was separated and acidified to pH1 with concentrated hydrochloric acid and then extracted with 10% MeOH in DCM (100ml x 3). The combined organic layers were dried over $MgSO_4$ and the solvent removed under vacuum to give a brown solid that was recrystallised from ethanol and dried under vacuum to give the title compound as pinkish crystals (2.63g, 41%). δH (DMSO-d^6) 8.74 (2H, s, pyr-H). δC (DMSO-d^6) 163.5, 147.7, 141.0, 126.7

INTERMEDIATE 7

N-Acetyl-*D*-thioproline-(*N*'-3,5-dichloro-isonicotinoyl)-*L*-4-aminophenylalanine methyl ester

A suspension of Intermediate 6 (0.50g, 2.6mmol) in DCM (10ml) was treated with thionyl chloride (1.55g, 0.95ml, 13.0mmol) and a drop of DMF, then heated to reflux for 1.5h. The volatiles were removed under vacuum to give a yellow solid that was dissolved in DCM. NMM (0.53g, 0.57ml, 5.2mmol) was added followed by Intermediate 5 (0.40g, 1.37mmol). The reaction was stirred for 16h then partitioned between DCM (20ml) and water (20ml). The aqueous layer was extracted with DCM, the combined organic layers washed with $NaHCO_3$ solution (50ml), dried over $MgSO_4$ and the solvent removed under vacuum, to give a brown gum, which was triturated with boiling methanol to give the title compound as a pale brown solid (0.13g). δH (DMSO-d^6, 300K) two rotamers observed: 10.85 (1H, s, NH), 8.79 (2H, s, pyr-H), 8.59 (d, *J* 8.2Hz) and 8.32 (d, *J* 8.2Hz), together

(1H, NH), 7.56 (2H, m, Ar-H), 7.22 (2H, m; Ar-H), 4.80-4.70 (m), and 4.58-4.44 (m) and 4.47 (d, J 8.6Hz) and 4.24 (d, J 9.6Hz), together (4H, 2xCH_α and NCH_2S), 3.31 (3H, s, CO_2CH_3), 3.20-2.82 (4H, m, $CH_\alpha C\underline{H_2}Ar$ and $CH_\alpha C\underline{H_2}S$), 2.06 (s) and 1.85 (s) together (3H, $COCH_3$). m/z (ESI, 60V) 525 (MH^+).

INTERMEDIATE 8

N-Boc-*D*-thioproline-*L*-tyrosine methyl ester

NMM (0.39g, 0.43ml, 3.9mmol), HOBT (0.57g, 4.2mmol), Boc-D-thioproline (0.91g, 3.9mmol), and EDC (0.75g, 3.9mmol) were added sequentially to a stirred solution of L-tyrosine methyl ester hydrochloride (0.82g, 3.5mmol) in dry DMF (10ml). The reaction mixture was stirred at room temperature for 0.75h. The DMF was removed in vacuo and the residue partitioned between EtOAc (70ml) and 10% aqueous Na_2CO_3 (30ml). The phases were separated and the aqueous phase re-extracted with EtOAc (2 x 20ml). The combined organic extracts were washed with brine (10ml), dried (Na_2SO_4) and evaporated in vacuo to afford the crude product as a viscous oil. Purification by flash chromatography (SiO_2; 5:95 MeOH/DCM) afforded the title compound as a white solid (1.1g, 76%): δH ($CDCl_3$) 6.96 (2H, d, J 8.5Hz, ArH), 6.85 (1H, br s NH), 6.72 (2H, d, J 8.5Hz, ArH), 5.95 (1H, br s, OH), 4.81 (1H, apparent dt, J 5.8, 8Hz, CHα-tyr), 4.73 (1H, br s, CHα-thiopro), 4.63 (1H, br d, J 9.0Hz, $NC\underline{H_A}H_BS$), 4.28 (1H, d, J 9.0Hz, $NCH_A\underline{H_B}S$), 3.71 (3H, s, $CO_2C\underline{H_3}$), 3.37-3.28 (1H, br m, $CHC\underline{H_A}H_BS$), 3.21-3.10 (1H, m, $CHCH_A\underline{H_B}S$), 3.09-2.97 (2H, m, CH_2Ar), and1.45 (9H, s, tBu); m/z (ESI, 27V) 411 (MH^+).

INTERMEDIATE 9

D-Thioproline-*L*-tyrosine methyl ester hydrochloride

Hydrogen chloride gas was briefly bubbled through a stirred solution of Intermediate 8 [1.0g in warm EtOAc (50ml)]. The reaction mixture was stirred at ambient temperature for 1h during which time the product precipitated from the solution. The solvent was removed *in vacuo* to afford the title compound as a white powder (0.85g): δH (CD_3OD) 8.83 (1H, d, J 8.3Hz, NH), 7.02 (2H, d, J 8.,5Hz, ArH), 6.71 (2H, d, J 8.5Hz, ArH), 4.74 (1H, m, CHα-tyr), 4.54 (1H, apparent t, 7.2Hz, CHα-thiopro), 4.36 (2H, m, $NC\underline{H_2}S$), 3.73 (3H, s, CO_2CH_3), 3.42 (1H, dd, J 7.4, 12Hz, $CHC\underline{H_A}H_BS$),

3.15 (1H, dd, J 5.2, 14Hz, C$\underline{H}_A$$H_B$Ar), 2.88 (1H, dd, J 9.6, 14Hz, C$H_A$$\underline{H}_B$Ar) and 2.79 (1H, dd, J 7.0, 12.0Hz, CHC$H_A$$\underline{H}_B$S); m/z (ESI, 27V) 311 MH+).

INTERMEDIATE 10

***N*-(Pyrid-3-ylacetyl)-*D*-thioproline-*L*-tyrosine methyl ester**

NMM (532mg, 580μL, 5.27mmol), HOBT (388mg, 2.87mmol) 3-pyridylacetic acid hydrochloride (457mg, 2.63mmol) and EDC (506mg, 2.63mmol) were added sequentially to a stirred solution of Intermediate 9 in dry DMF (15ml). The reaction mixture was stirred at room temperature for 5h. The solvent was removed *in vacuo* and the residue partitioned between EtOAc (75ml) and saturated aqueous $NaHCO_3$ (30ml). The phases were separated and the aqueous phase re-extracted with EtOAc (3 x 30ml). The combined organic extracts were washed with brine (10ml) dried (Na_2SO_4) and evaporated *in vacuo* to afford an off-white solid (1.06g). This was heated in boiling EtOAc (40ml) and, after cooling, the title compound was filtered off as a white powder (0.66g, 64%) δH (DMSO-d^6, 400K) 8.64 (1H, br s, O$\underline{H}$), 8.44 (2H, m, pyr-$\underline{H}$), 7.84 (1H, br d, J 7Hz, NH), 7.60 (1H, dd, J 2.1, 7.8Hz, pyr$\underline{H}$), 7.28 (1H, dd, J 4.7, 7.8Hz, pyr$\underline{H}$), 6.98 (2H, d, J 8.3Hz, Ar$\underline{H}$) 6.86 (2H, d, J 8.3Hz, Ar$\underline{H}$), 4.93 (1H, dd, J 4, 7.4Hz, CHαthiopro), 4.85 (1H, d, J 9.2Hz, NC$\underline{H}_A$$H_B$S), 4.54 (1H, ddd, J 6.0, 7.3, 8.2Hz, C$\underline{H}$αtyr), 4.45 (1H, d, J 9.2Hz, NC$H_A$$\underline{H}_B$S), 3.75 (1H, d, J 16Hz, C$\underline{H}_A$$H_B$pyr), 3.66 (1H, d, J 16Hz, C$H_A$$\underline{H}_B$pyr), 3.64 (3H, s, CO_2CH_3), 3.29 (1H, dd, J 7.4, 11.5Hz, CHC$\underline{H}_A$$H_B$S), 3.05-2.97 (2H, m, CHC$H_A$$\underline{H}_B$S and C$\underline{H}_A$$H_B$Ar) and 2.88 (1H, dd, J 8.2, 14.2Hz, C$H_A$$\underline{H}_B$Ar); m/z (ESI, 27V) 430 (MH+).

INTERMEDIATE 11

***N*-(Pyrid-3-ylacetyl)-*D*-thioproline-(*O*-2,4,6-trichlorobenzoyl)-*L*-tyrosine methyl ester**

Sodium hydride (61mg, 1.5mmol) was added to a solution of Intermediate 10 (0.50g, 1.2mmol) in anhydrous DMF (10ml). When the vigorous reaction had ceased 2,4,6-trichlorobenzoyl chloride (0.35g, 1.44mmol) was added and the reaction stirred for 16h at room temperature. The reaction was poured into saturated $NaHCO_3$ solution (50ml) and extracted with EtOAc (3x50ml). The combined organic layers were washed with saturated $NaHCO_3$ solution (2x20ml), brine (20ml) and dried over $MgSO_4$.

The solvent was evaporated *in vacuo* and the residue purified by chromatography (SiO_2; DCM/MeOH 95:5) to give the title compound as an orange oil (0.65g, 74%) containing about 30% of the diastereomer at the thioproline stereocentre. δH (DMSO-d^6, 390K) 8.43 (2H, m, pyr-H), 7.97 (1H, m, NH), 7.77 (2H, s, Ar-H), 7.62 (1H, m, pyr-H), 7.36-7.16 (5H, m, pyr-H, Ar-H), 4.92 (1H, m, CH_α-thiopro), 4.86 (1H, m, $NC\underline{H}_AH_BS$), 4.65 (1H, m, CH_α-tyr), 4.47 (1H, m, $NCH_A\underline{H}_BS$), 3.74 (2H, m, CH_2pyr), 3.66 (3H, s, CO_2CH_3), 3.36-2.98 (4H, m, $ArCH_2$ and $CHC\underline{H}_2S$). m/z (ESI, 30V) 638 (MH^+).

INTERMEDIATE 12

***N*-Boc-(*O*-pyrimidin-2-yl)-*L*-tyrosine methyl ester**

A solution of N-Boc tyrosine methyl ester (591mg, 2mmol) in DMF (5ml) was added to a suspension of sodium hydride (60% in oil, 88mg, 2.2mmol) in DMF (5ml) at room temperature. After 5min, a solution of 2-chloropyrimidine (288mg, 2.5mmol) in DMF (3ml) was added and the mixture stirred for 5h. The reaction mixture was quenched with water and the DMF evaporated *in vacuo*. The residue was dissolved in EtOAc (150ml) and washed with water (2 x 50ml) and brine (50ml), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by chromatography (SiO_2; EtOAc/hexane 60:40) to give the title compound as a colourless gum (470mg, 63%): δH ($CDCl_3$) 8.55 (2H, d, J 4.7Hz, HetArH), 7.21-7.11 (4H, m, ArH), 7.02 (1H, t, J 4.7Hz, HetArH), 5.00 (1H, br d, CONH), 4.62 (1H, br q, CHα), 3.72 (3H, s, CO_2CH_3), 3.17-3.06 (2H, m, $C\underline{H}_2Ar$) and 1.42 (9H, s, tBu); m/z (ESI, 15V) 374 (MH^+).

INTERMEDIATE 13

(*O*-Pyrimidin-2-yl)-*L*-tyrosine methyl ester hydrochloride

Gaseous HCl was bubbled through a solution of Intermediate 12 (460mg, 1.23mmol) in EtOAc (25ml) for about 30 seconds. After 20 min the EtOAc was removed *in vacuo* to give the title compound as a white foam. δH (DMSO, 300K) 8.63 (2H, d, J 4.9Hz, HetArH), 7.32-7.25 (3H, m, ArH + HetArH), 7.15 (2H, d, J 8.5Hz, ArH), 4.29 (1H, br q, CHα), 3.69 (3H, s, CO_2CH_3), 3.22 (1H, dd, J 6.0, 14.1Hz, $C\underline{H}_AH_BAr$) and 3.14 (1H, dd, J 7.1, 14.1Hz, $CH_A\underline{H}_BAr$).

INTERMEDIATE 14

***N*-Acetyl-*D*-thioproline-(*O*-pyrimidin-2-yl)-*L*-tyrosine methyl ester**

EDC (259mg, 1.35mmol) was added to a solution of Intermediate 13 (1.23mmol), N-acetyl-D-thioproline (215mg, 1.23mmol), HOBT (182mg, 1.35mmol) and NMM (285μl, 2.6mmol) in DCM (15ml). The reaction mixture was stirred at room temperature overnight then diluted with DCM (150ml). The DCM solution was washed with 10% citric acid (50ml), saturated aqueous $NaHCO_3$ (50ml) and water (50ml), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by chromatography (SiO_2; DCM/MeOH, 93:7) to give the title compound as a slightly yellow gum (484mg, 92%). δH (DMSO-d^6, 400K) 8.60 (2H, dd, J 4.8Hz, HetArH), 7.25 (2H, s, J 8.7Hz, ArH), 7.20 (1H, t, J 4.8Hz, HetArH), 7.09 (2H, d, J 8.7Hz, ArH), 4.83 (1H, dd, J 4.0, 7.4Hz, CHαthiopro), 4.77 (1H, d, J 9.2Hz, NC$H_A$$H_B$S), 4.63 (1H, dt, J 5.6, 8.3Hz, CHαtyr), 4.39 (1H, d, J 9.1Hz, NC$H_A$$H_B$S), 3.68 (3H, s, CO_2CH_3), 3.26 (1H, dd, J 7.4, 11.6Hz CHC$H_A$$H_B$S), 3.16 (1H, dd, J 5.7, 14.1Hz, C$H_A$$H_B$Ar), 3.09-2.99 (2H, m, C$H_A$$H_B$Ar + CHC$H_A$$H_B$S) and 2.00 (3H, s, CH_3CO); m/z (ESI, 27V) 431 (MH^+).

INTERMEDIATE 15

***N*-(Pyrid-3-ylacetyl)-*D*-thioproline-(*O*-2,6-dichlorobenzoyl)-*L*-tyrosine methyl ester**

To a suspension of NaH (60%, 103mg, 2.56mmol) in anhydrous DMF (25ml) under argon was added Intermediate 10 (1.0g, 2.33mmol) in one portion. After 3 min. 2,6-dichlorobenzoyl chloride (0.54mg, 0.37ml, 2.56mmol) was added and the mixture allowed to warm up to room temperature. After 2h at room temperature a further portion of NaH (60%, 19mg, 0.47mmol) and 2,6-dichlorobenzoyl chloride (0.067ml, 98mg, 0.47mmol) was added to the pale yellow mixture and the reaction stirred at room temperature over the weekend (60h). The reaction mixture was poured into half-saturated NH_4Cl/ice and EtOAc added. The layers were separated and the aqueous layer extracted with EtOAc (2 x 50ml). The combined organic layers were washed with saturated $NaHCO_3$ (1 x 100ml), brine (1 x 100ml) and dried over $MgSO_4$. The solvent was removed *in vacuo* to afford a pale yellow foam. Purification by flash chromatography (SiO_2; 1:99 to 3:97 MeOH/DCM) gave the title compound

as an off-white foam (1.1g, 78%). δH (DMSO-d^6, 400K) 8.48-8.43 (2H, m, pyr-H), 8.01 (1H, br d, NH), 7.63-7.52 (4H, m, Ar(Cl)-H and pyrH), 7.34 (2H, d, J 8.6Hz, ArH), 7.34-7.26 (1H, m, pyrH), 7.19 (2H, d, J 8.6Hz, ArH), 4.93 (1H, dd, J 7.3, 4.0Hz, CHαthiopro), 4.86 (1H, d, J 9.2Hz, NCH_AH_BS), 4.68-4.61 (1H, m, CHαtyr), 4.46 (1H, d, J 9.2Hz, NCH_AH_BS), 3.76 (1H, d, J 16Hz, CH_AH_Bpyr), 3.68 (1H, d, J 16Hz, CH_AH_Bpyr), 3.67 (3H, s, CO_2CH_3), 3.29 (1H, dd, J 11.6, 7.3Hz, $CHCH_AH_BS$), 3.19 (1H, dd, J 14, 5.7Hz, CH_AH_BAr) and 3.09-3.00 (2H, m, $CHCH_AH_BS$ and CH_AH_BAr).

INTERMEDIATE 16

_N_-Acetyl-_D_-thioproline-(_N'_-2,6-dichlorobenzoyl)-_L_-4-aminophenyl alanine methyl ester

NMM (104μg, 113ml, 1.02mmol), 2,6-dichlorobenzoyl chloride (216mg, 148μL, 1.02mmol) and 4-dimethylaminopyridine (10mg) were added sequentially to a stirred solution of Intermediate 5 (302mg, 0.86mmol) in dry DCM (10ml). The reaction mixture was stirred at room temperature for 18h under N_2. The solvent was removed *in vacuo* and the residue treated with 5% aqueous hydrochloric acid (~50ml). The obtained solid was collected by filtration, with further aqueous hydrochloric acid washing followed by water and diethyl ether washing. The product was treated with hot MeOH (~10ml) then cooled and filtered off to afford the title compound as a white powder (205mg, 45%): δH (DMSO-d^6) (two rotamers observed) 10.95 (1H, s, ArNHCO), 8.58 (d. J 7.9Hz) and 8.31 (d, J 8.2Hz) together (1H, CHNHCO), 7.69-7.45 (5H, m, ArH), 7.23-7.12 (2H, m, ArH), 4.81-4.65 (m) and 4.58-4.48 (m) and 4.23 (d, J 9.5Hz), together (4H, NCH_2S and CHα-thiopro and CHαPh), 3.64 (3H, s, CO_2CH_3), 3.18-2.75 (4H, m, $CHCH_2S$ and CH_2Ar), 2.05 (s) and 1.84 (s) together (3H, $COCH_3$); m/z (ESI, 27V) 524 (MH^+).

INTERMEDIATE 17

_N_-Boc-_D_-thioproline-(_O_-benzyl)-_L_-tyrosine methyl ester

NMM (1.73g, 1.9ml, 17.13mmol), HOBT (2.53g, 18.74mmol) N-Boc-D-thioproline (4.0g, 17.17mml) and EDC (3.30g, 17.19mmol) were added sequentially to a stirred solution of O-benzyl-L-tyrosine methyl ester hydrochloride (5.02g, 15.59mmol) in dry DMF (50ml). The reaction mixture was stirred at room temperature under N_2 for 3h. The DMF was

removed *in vacuo* and the residue partitioned between EtOAc (150ml) and 5% aqueous Na_2CO_3 (50ml). The phases were separated and the aqueous phase re-extracted with EtOAc (2 x 50ml). The combined organic extracts were washed consecutively with 5% aqueous hydrochloric acid (30ml), 5% aqueous Na_2CO_3 (30ml) and brine (20ml) then dried (Na_2SO_4) and evaporated *in vacuo* to afford the title compound as a straw coloured oil (7.8g). This was used without further purification but can be purified by flash chromatography (SiO_2; 2:98 MeOH/DCM). δH (DMSO-d^6), 7.48-7.28 (5H, m, ArH), 7.03 (2H, d, *J* 8.6Hz, ArH), 6.88 (2H, d, *J* 8.6Hz, ArH), 6.82 (1H, br s NH), 5.02 (2H, s, $PhCH_2O$), 4.81 (1H, apparent, dt, *J* 5.8Hz, CHα-tyr), 4.73 (1H, m, CHα-thiopro), 4.64 (1H, br d *J* 9Hz, NCH_AH_BS), 4.25 (1H, d, *J* 9.2Hz, NCH_AH_BS), 3.69 (3H, s, CO_2CH_3), 3.34 (1H, br d, *J* 11Hz, $CHCH_AH_BS$), 3.13 (1H, br d, $CHCH_AH_BS$) 3.06 (1H, d, *J* 5.8Hz, CH_2Ar) and 1.45 (9H, s ^{t}Bu); m/z (ESI, 15V) 501 (MH^+).

INTERMEDIATE 18

D-Thioproline-(*O*-benzyl)-*L*-tyrosine methyl ester

Intermediate 17 (8.2g) was stirred in trifluoroacetic acid (50ml) and DCM (50ml) at room temperature for 1h. The solvent was removed *in vacuo* and the residue partitioned between EtOAc (150ml) and saturated aqueous $NaHCO_3$ (50ml). The phases were separated and the aqueous phase re-extracted with EtOAc (32 x 50ml). The combined organic extracts were washed with brine (30ml), dried (Na_2SO_4) and evaporated *in vacuo*. The obtained solid was treated with diethyl ether (50ml) and filtered off with a little ether washing affording the title compound as white needles (5.3g, 81%): m.p. 138-140°. δH (1:1, $CDCl_3/CD_3OD$) 7.42-7.23 (5H, m, PhH), 7.03 (2H, d, *J* 8Hz, ArH), 6.86 (2H, d, *J* 8.7Hz, ArH), 5.02 (2H, s, OCH_2Ph), 4.68 (1H, dd, *J* 7.5, 5.5Hz, CHα-tyr), 4.10 (1H, d, *J* 9.6Hz, NCH_AH_BS), 3.96 (1H, d, *J* 9.6Hz, NCH_AH_BS), 3.96-3.94 (1H, m, CHα-thiopro), 3.69 (3H, s, CO_2CH_3), 3.13-3.04 (2H, m) and 3.01-2.92 (2H, m) together (4H, $CHCH_2S$ and CH_2Ar). m/z (ESI, 27V) 401 (MH^+).

INTERMEDIATE 19

N-(Pyrid-3-ylacetyl)-*D*-thioproline-(*O*-benzyl)-*L*-tyrosine methyl ester

HOBT (134mg, 0.99mmol), 3-pyridylacetic acid hydrochloride (157mg, 0.90mmol), and EDC (175mg, 0.90mmol) were added sequentially to a

stirred soution of Intermediate 18 (330mg, 0.83mmol) in dry DMF(5ml). The reaction mixture was stirred at room temperature for 6h. The DMF was removed *in vacuo* and the residue partitioned between EtOAc (50ml) and 5% aqueous Na_2CO_3 (30ml). The phases were separated and the aqueous phase re-extracted with EtOAc (2 x 30ml). The combined organic extracts were washed with brine (10ml), dried (Na_2SO_4) and evaporated *in vacuo*. The obtained glassy solid was chromatographed (SiO_2; 2.5:97.5 MeOH/DCM) to yield the title compound as a colourless foam (240mg, 56%): δH ($CDCl_3$) (two rotameric species) 8.52-8.31 (2H, br m, pyrH), 7.56-7.43 (distorted br d, J ~8Hz) and 7.40-7.23 (br m) and 7.27 (m) together (7H, PhH, pyrH and CONH), 7.01 (1H, m, pyrH), 6.98 (2H, d, J 8.3Hz, ArH), 6.84 (2H, d, J 8.3Hz, ArH), 5.08-4.88 (m) and 4.82-4.38 (m) together (6H, CH_2O, NCH_2S, CHα-thiopro and CHα-tyr), 3.78-3.62 (m and br s) and 3.44-2.92 (m) together (9H, CO_2CH_3, CH_2pyr, CH_2Ar and $CHCH_2S$); m/z (ESI) 520 (MH^+).

INTERMEDIATE 20

N-Acetyl-*D*-thioproline-*L*-(4-benzoylphenylalanine) methyl ester

HOBT (240mg, 1.78mmol), *N*-acetyl-*D*-thioproline (286mg, 1.63mmol) and EDC (313mg, 1.63mmol) were added sequentially to a stirred solution of *L*-4-benzoylphenylalanine methyl ester (420mg, 1.48mmol) in dry DMF (10ml). The reaction mixture was stirred at room temperature under N_2 for 2h. The DMF was removed *in vacuo* and the residue partitioned between EtOAc (70ml) and 5% aqueous Na_2CO_3 (30ml). The phases were separated and the aqueous phase re-extracted with EtOAc (2 x 20ml). The combined organic extracts were washed consecutively with 5% aqueous HCl (20ml), 5% aqueous Na_2CO_3 (10ml) and brine (10ml), then dried (Na_2SO_4) and evaporated *in vacuo* to afford the crude product. Chromatography (silica; 55:95 MeOH/EtOAc) afforded the title compound as a colourless oil (610mg, 93%): δH ($CDCl_3$,) (approximate 3:1 mixture of rotameric species) 7.8-7.7 (4H, m), 7.62-7.57 (1H, m), 7.52-7.45 (2H, m), 7.29-7.22 (2H, m), 7.10 and 6.70 (1H, d, J 7.7Hz), 5.05-5.00 (1H, narrow m), 4.94-4.82 (1H, m), 4.72 and 4.58 (1H, d, J 8.7Hz), 4.50 and 4.43 (1H, d, J 8.7Hz), 3.77 and 3.73 (3H, s), 3.45 (1H, dd, J 11.6, 2.9Hz), 3.40-3.05 (3H, m's), 2.16 and 1.90 (3H, s); and m/z (ESI, 27V) 441 (MH^+).

INTERMEDIATE 21

N-Acetyl-*D*-thioproline-(*N*'-2,6-dichlorobenzyl)-*L*-4-aminophenylalanine methyl ester

A solution of Intermediate 5 (1g, 2.85mmol), NMM (374mg, 407μl, 3.7mmol) and 2,6-dichlorobenzyl bromide (889mg, 3.70mmol) in dry DCM (20ml) was stirred at room temperature under N_2 for 18h. The reaction was diluted with DCM (80ml) and washed with saturated aqueous $NaHCO_3$ (30ml). The phases were separated and the aqueous layer extracted with DCM (2x30ml). The combined organic extracts were washed with brine (10ml), dried (Na_2SO_4) and evaporated *in vacuo*. The obtained yellow oil was purified by flash chromatography (silica; EtOAc) affording the title compound as a colourless glass (0.78g, 54%). δH (DMSO-d^6) (0.66:0.33 ratio of rotamers) 7.32 (2H, app.d, J 7.8Hz), 7.16 (1H, app.t, J 7.8Hz), 6.92 (2H, distorted t, J 8.4Hz), 6.83 and 6.48 (1H, br d, J 8.0Hz), 6.67 (2H, d, J 8.4Hz), 5.08-5.04 (0.66H, m), 4.81-4.68 (1.33H,m), 4.59-4.55 (2H, br , s), 4.55-4.4 (2H, m), 4.02-3.94 (0.66H, br s), 3.75 and 3.70 (3H, s), 3.42 (0.66H, dd), 3.27 (0.66H, dd), 3.16-2.90 (3H m), 2.15 and 1.84 (3H, s); m/z (ESI, 30V) 510 and 510 (MH^+).

INTERMEDIATE 22

N-(*N*-Acetyl-*D*-5,5-dimethyl-1,3-thiazolia-4-oyl)

NMM (111mg, 120μl, 1.10mmol), HOBT (162mg, 1.20mmol), Intermediate 42 (b) (223mg, 1.10mmol) and EDC (211mg, 1.10mmol) were added sequentially to a stirred solution of *O*-benzyl-*L*-tyrosine methyl ester hydochloride (322mg, 1mmol) in dry DMF (5ml). The reaction mixture was stirred at room temperature for 3h and crude product obtained therefrom as described for Intermediate 17. Chromatography (SiO_2, 60:40 to 90:10 EtOAc/ hexane) afforded the title compound as a colourless glass (355mg, 76%). δH ($CDCl_3$) 7.43-7.28 (5H, m), 7.03-6.94 (2H, m), 6.93-6.82 (2H, m), 6.64 and 6.32 (1H, d, J 8.0Hz), 5.04 and 5.03 (2H, s), 4.86-4.80 (1H, m), 4.64-4.46 (2H, m), 4.37 and 4.00 (1H, s), 3.74 and 3.72 (3H, s), 3.13-2.91 (2H, m's), 2.04 and 1.81 (3H, s), 1.48, 1.42 and 1.35 (6H, s); m/z (ESI, 60V) 471 (MH^+).

INTERMEDIATE 23

***N*-(4-Morpholinoacetyl)-*D*-thioproline-*O*-(2,6-dichlorobenzyl)-*L*-tyrosine methyl ester**

Bromoacetyl bromide (1.20g, 0.52ml, 5.97 mmol) was added dropwise to a stirred, ice-bath cooled solution of *D*-thioproline-*O*-(2,6-dichlorobenzyl) tyrosine methyl ester (2.80g, 5.97mmol) and NMM (0.603g, 0.66ml, 5.97 mmol) in dry DCM (40ml). The reaction mixture was stirred under N_2 for 2h. The reaction was partitioned between DCM (100ml) and 10% aqueous HCl (40ml). The phases were separated and the aqueous phase re-extracted with DCM (40ml). The combined organic extracts were washed consecutively with 10% aqueous HCl (20ml), water (20m) and brine (10ml), dried (Na_2SO_4) and evaporated *in vacuo*. The obtained oil was chromatographed (SiO_2; 50:50 to 65:35, EtOAc/hexane; applied in DCM) to afford the *N*-bromoacetyl derivative as a white foam (1.95g, 55%). (ESI, 60V) 589 (MH^+). This intermediate (840mg, 1.42mmol) was stirred with morpholine (248mg, 250μl, 2.84mmol) in MeOH (10ml) for 18h. The solvent was removed *in vacuo* and the residue partitioned between satuated aqueous $NaHCO_3$ (30ml) and EtOAc (70ml). The phases were separated and the aqueous phase re-extracted with EtOAc (3x30ml). The combined organic extracts were washed with brine (10ml), dried (Na_2SO_4) and evaporated *in vacuo*. The obtained crude oil was chromatographed [silica; DCM (400), MeOH (20), AcOH (3), H_2O (2)] to afford the title compound as a foam (620mg, 73%). δH (DMSO-d^6) (1:1 mixture of rotamers) 8.51 and 8.30 (1H, d, J 8.0Hz), 7.52 (2H, d, J 8.0Hz),7.42 (1H, d, J 8.0Hz), 7.13 (2H, t, J 8.0Hz), 6.95 (2H, d, J 8.0Hz), 5.18 (2H, s), 5.19-5.10 (0.5H, m), 4.90 (0.5H, d, J 9.0Hz), 4.80-4.72 (1H, m), 4.62-4.47 (1.5H, m), 4.24 (0.5H, d, J 9.0Hz), 3.62 (3H, s), 3.6-3.46 (4H, br m), 3.35-2.6 (6H, m) and 2.48-2.25 (4H, br m).

INTERMEDIATE 24

***L*-4-(Methylamino)phenylalanine methyl ester dihydrochloride**

Iodomethane (7.75g, 3.4ml, 54.6mmol) was added to a stirred solution of *N*-Boc-*L*-4-aminophenylalanine methyl ester (10.7g, 36.4mmol) in dry DCM (60ml), and stirred at room temperature for 24h. NMM (1.83g, 1.99ml, 18.1mmol) was added and the reaction stirred for 18h. The volatiles were removed *in vacuo* and the residue partitioned between

EtOAc (150ml) and saturated aqueous $NaHCO_3$ (100ml). The phases were separated and the aqueous phase extracted with EtOAc (100ml). The combined organic extracts were washed with brine (20ml), dried (Na_2SO_4) and evaporated *in vacuo* to afford a dark oil. This was a mixture of the desired mono N-methylated product contaminated with more polar starting material and less polar N,N-dimethylated by-product. Chromatography (SiO_2, 40:60 to 75:25 Et_2O/hexane) afforded the desired *N*-Boc-*L*-4-(methylamino)phenyl alanine methyl ester (3.1g) as a white crystalline solid. δH ($CDCl_3$) 6.92 (2H, d, J 8.0Hz), 6.53 (2H, d, J 8.0Hz), 4.94 (1H, br d, J 7.0Hz), 4.50 (1H, m), 3.70 (3H, s), 2.98 (1H, d, J 5.5Hz), 2.81 (3H, s) and 1.42 (9H, s). This intermediate (3.05g) was dissolved in methanol (100ml) and HCl gas bubbled through the solution for 30 seconds. The reaction mixture was allowed to stand for 1h. The volatiles were removed *in vacuo* to afford the title compound as an off white solid (2.56g, 25% over 2 steps). δH (CD_3OD) 7.60 (2H, d, J 8.0Hz), 7.52 (2H, d, J 8.0Hz), 4.41 (1H, t, J 6.8Hz), 3.80 (3H, s), 3.34 (2H, m) and 3.08 (3H, s).

INTERMEDIATE 25

N-Acetyl-*D*-thioproline-*L*-4-(methylamino)phenylalanine methyl ester

Intermediate 24 was reacted with *N*-acetyl-*D*-thioproline in a similar manner to that described for Intermediate 5. Chromatography (SiO_2; 3:97 to 5:95 MeOH/DCM) afforded the title compound as a white foam (1.34g). δH ($CDCl_3$) (0.66:0.33 ratio of rotamers) 6.98-6.82 (3H, m), 6.52 (2H, d, J 8.4Hz), 5.09-5.04 (0.66H, m), 4.80-4.70 (0.66H, m), 4.55 (0.66H, d, J 8.7Hz), 4.50-4.40 (0.33H x 2, obscured m), 4.41 (0.66H, d, J 8.7Hz), 3.74 (3H x 0.33, s), 3.70 (3H, x 0.66, s), 3.42 (0.66H, dd), 3.27 (0.66H, dd), 3.14-2.93 (2.66H, m), 2.79 (3H, s), 2.16 (3H x 0.66, s) and 1.88 (3H x 0.33); m/z (ESI) 366 (MH^+).

INTERMEDIATE 26

N-(Diphenylmethylene)-4-(carbobenzyloxy)phenylalanine ethyl ester

A mixture of *N*-(diphenylmethylene)glycine ethyl ester (6.6g, 24.9mmol), benzyl 4-(bromomethyl)benzoic acid (7.61g, 24.9mmol) and potassium carbonate (50mmol, 6.9g) in acetonitrile (300ml) was refluxed overnight. The solvent was removed *in vacuo* and the residue partioned between

EtOAc and water. The aqueous layer was extracted with EtOAc and the combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give the title compound as an oil (13.0g) δH ($CDCl_3$) 7.90 (2H, d, J 8.3Hz), 7.58 (2H, d, J 7.3Hz), 7.50-7.25 (11H, m), 7.14 (2H, d, J 8.1Hz), 6.65 (2H, d, J 6.8Hz), 5.33 (2H, m), 4.30-4.15 (3H, br m), 3.32 (2H, v br s) and 1.26 (3H, t, J 7.1Hz); m/z (ESI, 60V) 492 (MH^+).

INTERMEDIATE 27

4-(Carbobenzyloxy)phenylalanine ethyl ester

A solution of Intermediate 26 (13.0g) in dilute hydrochloric acid (2M, 20ml) and THF (200ml) was stirred for 2h at room temperature. The solvent was removed *in vacuo*. The residue was triturated wth Et_2O to give a white solid, and recrystallisation from EtOH/EtOAc gave the HCl salt of the title compound as a white solid (4.24g, 46.8%). The mother liquors were concentrated *in vacuo* to give a glassy solid, which was dissolved in EtOAc and washed with saturated $NaHCO_3$. The aqueous layer was re-extracted with EtOAc and the combined organic extracts dried (Na_2SO_4) and evaporated *in vacuo*. Chromatography (SiO_2, EtOAc) gave the title compound as a glassy solid (2.75g, 33.8%). For the HCl salt: δH (DMSO-d^6) 7.96 (2H, dd, J 6.6, 1.7Hz), 7.48-7.37 (7H, m), 5.35 (2H, s), 4.29 (1H, dd, J 7.7, 5.1Hz), 4.10 (2H, q, J 7.1Hz), 3.27 (1H, dd, J 14.0, 5.9Hz), 3.15 (1H, dd, J 14.0, 7.7Hz) and 1.08 (3H, t, J 7.1Hz); m/z (ESI, 60V) 328 (MH^+).

INTERMEDIATE 28

***N*-Boc-4-(carbobenzyloxy)phenylalanine ethyl ester**

NaOH (1M, 15.1ml) was addd to Intermediate 27 (5g, 13.75mmol) in *tert*-butanol (110ml). After a solution had been obtained, a solution of di-*tert*-butyl dicarbonate (3.6g, 1 equivalent) in *tert*-butanol (50ml) was added in portions. The reaction mixture was stirred at room temperature overnight then the solvent removed *in vacuo*. The resulting oil was taken up in water (200ml) and the pH adjusted to pH3 with citric acid (10%). After extraction [EtOAc (3 x 250ml)], the combined organic extracts were washed with saturated $NaHCO_3$ and water, dried (Na_2SO_4) and concentrated *in vacuo* to give the title compound as a yellow oil (6.1g, 100%). δH ($CDCl_3$, 300MHz) 7.9 (2H, d, J 8.2Hz), 7.5-7.35 (7H, m containing d, J 8.2Hz), 5.3

(2H, s), 4.20-4.0 (3H, m), 3.1-2.9 (2H,m), 1.3 (9H, s) and 1.2 (3H, m); m/z (ESI, 60V) 450 (MNa^+).

INTERMEDIATE 29

***N*-Boc-4-carboxyphenylalanine ethyl ester**

A mixture of Intermediate 28 (6.1g, 14.3mmol) and palladium on charcoal (10%Pd, 610mg) in ethanol (150ml) was stirred under a hydrogen atmosphere (balloon) at room temperature overnight. The catalyst was removed by filtration and the filtrate concentrated *in vacuo* to give the title compound as a white waxy solid (4.2g. 87%) δH ($CDCl_3$) 8.0 (2H, d, J 8.0Hz), 7.3 (2H, d, J 8.0Hz), 4.8 (1H, s), 4.4 (1H, m), 4.1 (2H,m), 3.2-3.1 (1H, m), 3.0-2.8 (1H, m), 1.3 (9H, s) and 1.2 (3H,m); m/z (ESI) 360 (MNa^+).

INTERMEDIATE 30

***N*-Boc-4-[(3,5-dichlorophenyl)carboxamido]phenylalanine ethyl ester**

Carbon tetrachloride (4.3ml, 44.5mmol) was added to a solution of Intermediate 29 (1.5g, 4.45mmol) and triphenylphosphine (1.4g, 5.34mmol) in acetonitrile (80ml). The mixture was stirred for 2h at room temperature. 3,5-Dichloroaniline (1.44g, 8.9mmol) was added and the reaction continued at room temperature for 20h. The solvent was removed *in vacuo* and the residue partitioned between water and EtOAc. The aqueous layer was re-extracted with EtOAc and the combined organic extracts washed with dilute HCl, water and saturated $NaHCO_3$, dried (Na_2SO_4) and concentrated *in vacuo*. Chromatography (SiO_2; EtOAc/ hexane, 1:4) gave the title compound as an off-white solid (1.20g, 56%), δH ($CDCl_3$) 7.96 (1H, brs), 7.76 (2H, d, J 8.3Hz), 7.62 (2H, d, J 1.5Hz), 7.24 (2H, d, J 8.5Hz), 7.13 (1H, t, J 1.5Hz),5.03 (1H, v br), 4.55 (1H, br m), 4.17 (2H,q, J 7.1Hz), 3.2-3.0 (2H, br m), 1.42 (9H, s) and 1.42 (3H, t, J 7.1Hz); m/z (ESI, 60V) 503 (MNa^+).

INTERMEDIATE 31

***N*-Boc-4-(*N'*-thioacetyl)amino-*L*-phenylalanine methyl ester**

To a solution of *N*-Boc-4-(*N'*-acetyl)amino-*L*-phenylalanine methyl ester (1.64g, 4.88mmol) in THF was added Lawesson's Reagent (1.08g, 2.68mmol, 0.55 eq). The resulting suspension was heated to reflux for 3h

and then the reaction mixture was left stirring at room temperature overnight. The volatiles were then removed *in vacuo* and the oil obtained purified by column chromaography (SiO_2; DCM/EtOAc 100:0 to 80:20) to give the title compound as a yellow oil (1.72g, 100%) δH ($CDCl_3$) 9.93 (br s) and 9.52 (br s) together (1H, NHAr), 7.60 (2H, d, J 8.3Hz, ArH), 7.16-7.03 (2H, m, ArH), 5.13-5.05 (1H, m, NHBoc), 4.54-4.43 (1H, m, CH), 3.65 (s) and 3.67 (s) together (3H, CO_2Me), 3.13-2.90 (2H, m, CH_2), 2.62 (s) and 2.52 (s) together (3H, $CSCH_3$) and 1.36 (9H, s, ^tBu); m/z (ESI, 60V) 353 (MH^+).

INTERMEDIATE 32

***N*-Boc-*O*-(trifluoromethylsulphonyl)-*L*-tyrosine methyl ester**

Trifluoromethanesulphonic anhydride (4ml, 23mmol) was added to a mixture of *N*-Boc tyrosine methyl ester (5.9g, 20mmol) and pyridine (8ml, 100mmol) in DCM (30ml) at 0°. After 30min the reaction mixture was diluted with water (60ml) and DCM (100ml) and washed with aqueous NaOH (0.5M, 50ml), water (60ml), citric acid (10% solution, 2 x 75ml) and water (60ml), dried (Na_2SO_4) and evaporated *in vacuo*. Purification by column chromatography (SiO_2; EtOAc/hexane, 2:1) gave the title compound (7.76g, 91%) as a colourless oil which solidified on standing. δH ($CDCl_3$) 7.25-7.18 (4H, m, ArH), 5.01 (1H, br d, CONH), 4.60 (1H, br q, CHα), 3.71 (3H, s, CO_2Me), 3.17 (1H, dd, J 13.8, 5.8Hz, CH_AH_BAr), 3.03 (1H, dd, J 13.6, 6.3 Hz, CH_AH_BAr) and 1.41 (9H, s, ^tBu); m/z (ESI, 15V) 428 (MH^+).

INTERMEDIATE 33

***N*-Boc-4-phenyl-*L*-phenylalanine methyl ester**

Tetrakis(triphenylphosphine)palladium (0) (3 mol %, 69mg) was added to a nitrogen purged mixture of Intermediate 32 (854mg, 2mmol), phenylboronic acid (488mg, 4mmol) and potassium carbonate (414mg, 3mmol) in toluene (20ml). The mixture was heated at 85-90° for 2h then diluted with EtOAc (150ml) and washed with saturated aqueous $NaHCO_3$ (50ml), water (50ml), citric acid (10%, 50ml), water (50ml) and brine (50ml), dried (Na_2SO_4) and evaporated *in vacuo*. Column chromatography (SiO_2; EtOAc/hexane; 20:80) gave the title compound (685mg, 96%) as a colourless oil which solidified on standing. δH ($CDCl_3$,

300MHz) 7.60-7.20 (9H, m, ArH), 5.07 (1H, br d, J 8.0Hz, CONH), 4.65 (1H, br q, CHα), 3.75 (3H, s, CO_2Me), 3.19 (1H, dd, J 13.8, 5.8Hz, C$\underline{H}_A$$H_B$Ar), 3.10 (1H, dd, J 13.8, 6.1Hz, CH$_A$$\underline{H}_B$Ar) and 1.44 (9H, s, ^{t}Bu); m/z (ESI,15V) 356 (MH^+),

INTERMEDIATE 34

***N*-Boc-4-(3-prop-1-enyl)-*L*-phenylalanine methyl ester**

Bistriphenylphosphine palladium (II) chloride (70mg, 0.1mmol) was added to a nitrogen purged mixture of Intermediate 32 (21.4g, 5mmol), allyltributyltin (1.55ml, 5mmol), and lithium chloride (425mg, 10mmol) in DMF (15ml). The mixture was heated at 90° for 1h then evaporated *in vacuo*. The residue was dissolved in Et_2O (200ml) and washed with water (2 x 50ml) and saturated potassium fluoride (50ml), dried (Na_2SO_4) and evaporated *in vacuo*. Purification by column chromatography (SiO_2; EtOAc/hexane; 10:90 to 20:80) gave the title compound (1.49g, 94%) as a colourless oil which solidified on standing. δH ($CDCl_3$) 7.12 (2H, d, J 8.1Hz,ArH), 7.05 (2H, d, J 8.0Hz, ArH), 6.02-5.88 (1H, m, $CH_2C\underline{H}=CH_2$), 5.10-5.04 (2H, m, $CH_2CH=C\underline{H}_2$), 4.95 (1H, v br d, CONH), 4.57 (1H, br q, CHα), 3.71 (3H, s,CO_2Me), 3.36 (2H, br d, J 6.7Hz, $C\underline{H}_2CH=CH_2$), 3.12-2.95 (2H, m, $CHC\underline{H}_2Ar$), and 1.42 (9H, s, ^{t}Bu); m/z (ESI, 15V) 320 (MH^+).

INTERMEDIATE 35

***N*-Boc-4-(2-benzo[*b*]furanyl)-*L*-phenylalanine methyl ester**

Tetrakis(triphenylphosphine)palladium(0) (347mg, 30mol%) was added to a nitrogen purged mixture of Intermediate 32 (427mg, 1mmol) benzo[*b*]furan-2-boronic acid (324mg, 2mmol) and potassium carbonate (207mg, 1.5mmol) in toluene (10ml). The mixture was heated at 90° for 4h, diluted with EtOAc (100ml), washed with saturated $NaHCO_3$ (30ml), water (30ml), citric acid (10%, 30ml), water (30ml) and brine (30ml), dried (Na_2SO_4) and evaporated *in vacuo*. Column chromatography (SiO_2; DCM) gave the title compound (277mg, 70%) as a white waxy solid. δH ($CDCl_3$) 7.79 (2H, d, J 8.3Hz, ArH), 7.59-7.50 (2H, m, ArH), 7.31-7.20 (4H, m, ArH), 6.99 (1H, s, C=C$\underline{H}$), 5.04 (1H, br d J 7.7Hz, CONH), 4.63 (1H, br q, CHα), 3.73 (3H, s,CO_2Me), 3.17 (1H, dd, J 13.8, 5.7Hz, C$\underline{H}_A$$H_B$Ar), 3.08 (1H, dd, J 13.7, 6.0Hz, CH$_A$$\underline{H}_B$Ar) and 1.43 (9H, s,^{t}Bu); m/z (ESI, 15V) 396 (MH^+).

INTERMEDIATE 36

***N*-Boc-4[2-(1-phenylethenyl)]phenylalanine methyl ester**

A mixture of *N*-Boc-4-iodo-*L*-phenylalanine methyl ester (1.22g, 3mmol) (Lei, H *et al*, J. Org. Chem (1994), 59, 4206-4210), palladium (II) acetate (67mg, 0.3mmol), tetrabutylammonium chloride (1.07g, 3.6mmol), tri(*O*-tolyl)phosphine (183mg, 0.6mmol), potassium carbonate (2.07g, 15mmol) and styrene (51mg, 4.5mmol) was heated in DMF (20ml) at 90° for 22h. The solvent was removed *in vacuo*, the residue dissolved in EtOAc (100ml) and washed with water (30ml), dilute HCl (1M, 30ml), saturated $NaHCO_3$ (30ml) and water (30ml), dried (Na_2SO_4) and evaporated *in vacuo*. Column chromatography (SiO_2; MeOH/DCM, 1:99) gave the title compound (500mg, 44%) as a light brown solid. δH ($CDCl_3$) 7.52-7.08 (11H, m, ArH + CH=CH), 4.97 (1H, br d, CONH), 4.60 (1H, br q, CH_α), 3.72 (3H, s, CO_2Me), 3.20-3.00 (2H, m, CH_2Ar) and 1.49 (9H, s, ^tBu); m/z (ESI, 27V) 382 (MH^+).

INTERMEDIATE 37

***N* Boc-4-(3-pyridyl)phenylalanine methyl ester**

A mixture of *N*-Boc-4-iodo-*L*-phenylalanine methyl ester (810mg, 2mmol, Lei, H *et al*, *ibid*) tetrakis(triphenylphosphine)palladium (0) (231mg, 0.2mmol), aqueous sodium carbonate (4mmol, 2ml of a 2M solution) and diethyl(3-pyridyl)borane (294mg, 2mmol) in dimethoxyethane (30ml) was refluxed for 6hr. The solvent was removed *in vacuo*, the residue dissolved in EtOAc (100ml) and washed with water (30ml) aqueous sodium thiosulphate (20ml) and brine (30ml) dried (Na_2SO_4)and evaporated *in vacuo*. Purification by column chromatography (SiO_2, EtOAc/hexane 30:70) gave the title compound (335mg,47%) as a yellow oil. δH ($CDCl_3$) 8.81 (1H, d, J 1.7Hz, PyrH), 8.56 (1H, dd, J 4.8, 1.6Hz, PyrH), 7.84 (1H, dt, J 7.9, 2.0Hz, PyrH), 7.49 (2H, d, J 8.2Hz, ArH), 7.34 (1H, ddd, J 7.9, 4.8, 0.6Hz, PyrH), 7.23 (2H, d, J 8.2Hz, ArH), 5.09 (1H, br d, J 7.8Hz, CONH), 4.62 (1H, br q, J 6.8Hz, CHα), 3.73 (3H, s, CO_2Me), 3.18 (1H, dd, J 13.8, 5.6Hz, $C\underline{H}_AH_BAr$), 3.07 (1H, dd, J 13.8, 5.8Hz, $CH_A\underline{H}_BAr$) and 1.40 (9H, s, ^tBu); m/z (ESI, 15V) 357 (MH^+).

INTERMEDIATE 38

2,6-Dichlorophenylacetylene

The title compound was prepared from 2,6-dichlorobenzaldehyde by the method of E. J. Corey and P. L. Fuchs, Tetrahedron Letters, (1972), 3769-3772 as off-white needles (hexane). m.p. 97-98°. δH ($CDCl_3$) 7.35-7.32 (2H, m, ArH), 7.20 (1H, dd, J 8.9, 7.2Hz, ArH) and 3.68 (1H, s, C≡CH); m/z (ESI) 170 (MH^+).

INERMEDIATE 39

***N*-Acetyl-*D*-thioproline-4-(2,6-dichlorophenylacetylene)-*L*-phenylalanine methyl ester**

A solution of *N*-acetyl-*D*-thioproline-4-iodo-*L*-phenylalanine methyl ester (4.62mg, 1mmol), [prepared from *N*-Boc-4-iodo- *L*-phenylalnine methyl ester (Lei, H *et al*, *ibid*) deprotected by a similar method to that described for Intermediate 13 and then reacted with *N*-acetyl-*D*-thioproline according to the method described for Intermediate 14] in triethylamine (5ml) and toluene (10ml) was purged with nitrogen. Bis(triphenylphosphine) palladium dichloride (36mg, 5mol%) and copper (I) iodide (20mg, 10 mol%) were added. A solution of Intermediate 38 (257mg, 1.5mmol) in toluene (5ml) was added over a period of 2h via syringe pump. The mixture was stirred for a further 1h at room temperature, then diluted with EtOAc (100ml) and washed with dilute HCl (30ml) and brine (30ml), dried (Na_2SO_4) and evaporated *in vacuo*. Purification by column chromatography (SiO_2; MeOH/DCM, 3:97 to 5:95) gave the title compound (452mg, 90%) as an orange solid. Recrystallisation from EtOAc gave an off-white solid (220mg). δH (DMSO-d^6, 300K) (mixture of two rotameric species observed) 8.62 (d, J 8.3Hz) and 8.34 (d, J 8.1Hz) (together 1H, CONH), 7.60 (2H, d, J 8.3Hz, Cl_2ArH), 7.51-7.49 (2H, m, ArH), 7.43 (1H, dd, J 8.9. 7.5Hz, Cl_2ArH), 7.35-7.29 (2H, m, ArH), 4.8-4.7 (2H, m, CHα + NC$\underline{H}_A$$H_B$S), 4.57-4.5 (1H, m, CHα), 4.47 (d, J 8.7Hz) and 4.23 (d, J 9.5Hz) (together 1H, NC$H_A$$\underline{H}_B$S), 3.65 (3H, s, CO_2Me), 3.35-2.80 (4H, m, 2 × CH$\underline{H}_2$) and 2.06 and 1.85 (3H, each s, $COCH_3$); m/z (ESI) 505 (MH^+).

INTERMEDIATE 40

***N*-Boc-4-(phenylacetylene)-*L*-phenylalanine methyl ester**

The title compound was prepared in a similar manner to Intermediate 39 using *N*-Boc-4-iodo-*L*-phenylalanine methyl ester and phenylacetylene. Purification by column chromatography (SiO_2; EtOAc/hexane, 20:80) gave the title compound as a yellow gum (1.45g, 77%). δH (DMSO-d^6) 7.55-7.27 (10H, m, ArH + CONH), 4.25-4.18 (1H, m, CHα), 3.62 (3H, s, CO_2Me), 3.04 (1H, dd, J 13.8, 5.1Hz, $C\underline{H}_AH_BAr$), 2.89 (1H, dd, J 13.7, 10.1Hz, $CH_A\underline{H}_BAr$) and 1.33 (9H, s,^{t}Bu); m/z (ESI, 30V) 380 (MH^+).

INTERMEDIATE 41

***N*-Boc-4-[2-(1-phenylethyl)]-*L*-phenylalanine methyl ester**

A mixture of Intermediate 40 (340mg, 0.9mmol) and palladium on charcoal (10% Pd wt/wt. 300mg) in methanol (10ml) was stirred under a hydrogen atmosphere (balloon) overnight. The catalyst was filtered off and the filtrate evaporated *in vacuo*. Column chromatography (SiO_2, EtOAc/hexane, 20:80) gave the title compound as a colourless gum (255mg, 74%). δH ($CDCl_3$, 300MHz) 7.31-7.02 (9H, m, ArH), 4.96 (1H, br d, CONH), 4.59 (1H, br q, CHα), 3.71 (3H, s, CO_2Me), 3.12-2.98 (2H, m, $CHC\underline{H}_2Ar$), 2.90 (4H, s, $C\underline{H}_2C\underline{H}_2$) and 1.43 (9H, s,^{t}Bu); m/z (ESI, 15V) 384 (MH^+).

INTERMEDIATE 42

a) *N*-Acetyl-5,5-*L*-dimethyl-1,3-thiazolidine-4-carboxylic acid

Acetic anhydride (614μl, 6.5mmol) was added to a suspension of *L*-5,5-dimethylthiazolidine-4-carboxylic acid (1g, 6.20mmol) in DMF (6ml). The mixture was stirred for 2h at room temperature to give a colourless solution. The solvent was removed *in vacuo* to give a white solid. Recrystallisation (acetone) gave the title compound as white cubes (585mg, 47%). δH (DMSO-d^6, 300K) (2 rotameric species observed) 4.80 (d J 8.8Hz) and 4.70 (d, J 9.9Hz) together (1H, $NC\underline{H}_AH_BS$), 4.71 (d, J 8.7Hz) and 4.50 (3, J 9.9Hz) together (1H, $NCH_A\underline{H}_BS$), 4.47 (s) and 4.25 (s) together (1H, CHα), 2.06 (s) and 1.93 (s) together (3H, $COCH_3$),1.53 (s) and 1.51 (s) together (3H, $C\underline{Me}_AMe_BS$), 1.41 (s) and 1.37 (s) together (3H, $CMe_A\underline{Me}_BS$) (acid proton not observed).

b) *N*-Acetyl-5,5-*D*-dimethyl-1,3-thiazolidine-4-carboxylic acid

The title compound was prepared using the same procedure from the corresponding *D*-acid .

INTERMEDIATE 43

***N*-(Pyrid-3-ylacetyl)-*D*-thioproline-*O*-(2,4,6-trichlorobenzyl)-*L*-tyrosine methyl ester**

A solution of Intermediate 10 (429mg, 1mmol) in DMF (5ml) was added to a suspension of sodium hydride (60% in mineral oil, 44mg, 1.1mmol) in DMF (5ml) at 0°. After 10min a solution of Intermediate 45 (302mg, 1.1mmol) in DMF (5ml) was added. The reaction mixture was stirred at 0° for 2h then at room temperature for 1h, quenched with water (~1ml) and the solvents removed *in vacuo*. The residue was dissolved in EtOAc (150ml) and washed with water (2 x 50ml) and brine (50ml), dried (Na_2SO_4) and evaporated *in vacuo*. Column chromatography (SiO_2: $MeOH/CH_2Cl_2$, 8:92) gave the title compound (435mg, 70%). δH (DMSO-d^6, 300K) (2 rotameric species observed) 8.75 (d, J 7.9Hz, CONH) and 8.44-8.35 (m) together (3H, 2 x PyrH + CONH), 7.76 (2H,s, Cl_3ArH_2), 7.63-7.54 (1H, m, PyrH), 7.34-7.30 (1H, m, PyrH), 7.20-7.11 (2H, m, ArH), 6.94-6.90 (2H, m, ArH), 5.13 (s) and 5.11 (s) together (2H, OCH_2Ar), 4.88-4.74 (2H, m, CHα + $NC\underline{H}_AH_BS$), 4.6-4.45 (m) and 4.29 (d, J 9.7Hz) together (2H, $NCH_A\underline{H}_BS$ + CHα), 3.83 (2H, s, $PyrC\underline{H}_2CO$), 3.63 (3H, s, CO_2Me), 3.20-2.69 (4H, m, 2 x $CHC\underline{H}_2$) (acid proton not observed); m/z (ESI, 60V) 622 (MH^+).

INTERMEDIATE 44

2,4,6-Trichlorobenzylalcohol

A solution of lithium aluminium hydride (1M in THF, 18ml, 18mmol) was added to a solution of 2,4,6-trichlorobenzoyl chloride (4.35g, 17.8mmol) in THF (70ml) at 0°. After 1h, water (685μl), aqueous NaOH (3M, 685μl) and water (2.06ml) were added. The mixture was stirred vigorously for 1h, the precipitate filtered off and the filtrate evaporated *in vacuo* to give a yellow solid. Recrystallisation from diisopropylether gave the title compound as white needles (2.63g, 70%), m.p. 100-101°. δH ($CDCl_3$) 7.35 (2H, s, ArH), 4.91 (2H, br s, $C\underline{H}_2OH$), 2.07 (1H, br s, $CH_2O\underline{H}$).

INTERMEDIATE 45

2,4,6-Trichlorobenzylbromide

Triphenylphosphine (1.57g, 6mmol) and carbon tetrabromide (1.99g, 6mmol) were added to a solution of Intermediate 44 (1.06g, 5mmol) in Et_2O (25ml). The mixture was stirred at room temperature overnight. The precipitate was filtered off and the filtrate evaporated *in vacuo*. Chromatography (SiO_2, DCM) gave the title compound as a mobile colouless oil which crystallised on standing (1.17g, 85%) m.p. 51-52°, δH ($CDCl_3$) 7.35 (2H, s, ArH) and 4.70 (2H, s,CH_2Br).

INTERMEDIATE 46

***N*-Acetyl-*D*-thioproline-*O*-(2-chloropyrimidin-4-yl)-*L*-tyrosine methyl ester**

A solution of *N*-acetyl-*D*-thioproline-*L*-tyrosine methyl ester (1.76g, 5mmol), [prepared from *N*-acetyl-*D*-thioproline and tyrosine methyl ester by a similar method to the preparation of Intermediate 5] in DMF (10ml) was added to a suspension of sodium hydride (60% in mineral oil, 210mg, 5.25mmol) in DMF (5ml) at room temperature. After 10 min a solution of 2,4-dichloropyrimidine (782mg, 5.25mmol) in DMF (5ml) was added. After 1h water (1ml) was added and the solvent evaporated *in vacuo*. The residue was dissolved in EtOAc (200ml) and washed with water (3 x 50ml) and brine (30ml), dried (Na_2SO_4) and evaporated *in vacuo*. Chromatography (SiO_2, MeOH/DCM 5:95) gave the title compound as a white foam (1.59g, 68%). δH (DMSO-d^6, 400K) 8.56 (1H, d, J 5.7Hz, PyrH), 7.9 (1H, br d, CONH),7.32 (2H, d,J 8.7Hz, ArH), 7.15 (2H, d, J 8.7Hz, ArH), 6.99 (1H, d, J 5.7Hz, PyrH), 4.83 (1H, dd, J 7.4, 3.9Hz, CHαthiopro), 4.77 (1H, d, J 9.2Hz, NCHH$_B$S), 4.64 (1H,dt, J 8.5, 5.6Hz, CHαtyr),4.39 (1H, d, J 9.2Hz, NCH$_A$H$_B$S), 3.67 (3H, s, CO_2Me), 3.26 (1H, dd, J 11.6, 7.4Hz, CHCH$_A$H$_B$S), 3.19 (1H, dd, J 14.0, 5.7Hz, CHCH$_A$H$_B$Ar), 3.09-3.00 (2H, m, CHCH$_A$H$_B$S + CHCH$_A$H$_B$Ar) and 2.00 (3H, s,$COCH_3$); m/z (ESI, 15V) 465 (MH^+).

INTERMEDIATE 47

***N*-Acetyl-*D*-thioproline-*O*-[2-(4-methoxythiophenoxy)pyrimidin-4-yl]*L*-tyrosine methyl ester**

4-Methoxythiophenol (129µl, 1.05mmol) was added to a suspension of sodium hydride (42mg, 1.05mmol) in DMF(5ml) at 0°. After 10 min a solution of Intermediate 46 (465mg, 1mmol) in DMF (5ml) was added. The mixture was stirred at room temperature overnight. The solvent was removed *in vacuo*, the residue dissolved in EtOAc (100ml) and washed with water (2 x 50ml) and brine (30ml), dried (Na_2SO_4) and evaporated *in vacuo*. Column chromatography (SiO_2, MeOH/DCM, 5:95) gave the title compound as a colourless gum (327mg, 58%). δH (DMSO-d^6, 300K) (2 rotameric species observed) 8.63 (d, *J* 7.9Hz) and 8.4 (d) together (1H, CONH), 8.40 (1H, d, *J* 5.7Hz, pyrH), 7.40 (2H, d, *J* 8.1Hz, ArH),7.22 (2H, t, *J* 7.5Hz, ArH), 7.05-7.01 (2H, m, ArH), 6.93 (2H, d, *J* 8.9Hz,ArH),6.69 (1H, d, *J* 5.7Hz, PyrH), 4.78-4.68 (2H, m, CHα + $NC\underline{H}_AH_BS$), 4.6-4.45 (1H, m, CHαtyr), 4.46 (d, *J* 8.6Hz) and 4.23 (d, *J* 9.7Hz) together (1H, $NCH_A\underline{H}_BS$), 3.80 (3H, s, ArOMe),3.65 (s) and 3.64 (s) together (3H, CO_2Me), 3.18-2.72 (4H, m, 2 x $CHC\underline{H_2}$), 2.05 (s) and 1.84 (s) together (3H, $COCH_3$); m/z (ESI, 15V) 569 (MH^+).

INTERMEDIATE 48

***N*-Boc-*N'*-phthaloyl-4-amino-*L*-phenylalanine methyl ester**

Phthaloyl dichloride (3.78ml, 26.25mmol) was added to a mixture of *N*-Boc-4-amino-*L*-phenylalanine methyl ester (7.35g, 25mmol), NMM (6.05ml, 55ml) and 4-dimethylaminopyridine (300mg, 2.5mmol) inTHF (125ml) at room temperature. The mixture was stirred at room temperature for 5 days. The bulk of the THF was removed *in vacuo*, the residue diluted with EtOAc (800ml) and washed with dilute HCl (100ml) and brine (100ml), dried (Na_2SO_4) and evaporated *in vacuo* to give a pale yellow solid. Recrystallisation from EtOAc gave the title compound as white needles (7.91g, 75%) m.p. 171-172°. δH (DMSO-d^6) 8.76-8.11 (4H, m, ArH), 7.35-7.23 (5H, m, ArH + CONH), 4.2 (1H,m, CHα), 3.62 (3H, s, CO_2Me), 3.05-2.84 (2H, m,$C\underline{H}_2Ar$) and 1.33 (9H, s, ^tBu); m/z (ESI, 60V) 425 (MH^+).

INTERMEDIATE 49

N-Boc-*N*-methyl-*N'*-phthaloyl-4-amino-*L*-phenylalanine methyl ester

A solution of Intermediate 48 (7.96, 18.8mmol) in DMF (90ml) was added via cannula to a suspension of sodium hydride (60% in mineral oil, 827mg, 20.68mmol) and methyl iodide (2.34ml, 37.6mmol) in DMF (100ml) at 0°. The mixture was allowed to warm to room temperature and stirred overnight. Water (~2ml) was added and the solvent removed *in vacuo*. The residue was dissolved in EtOAc (400ml) and washed with water (2 x 100ml) and brine (50ml), dried (Na_2SO_4) and evaporated *in vacuo*. Column chromatography (SiO_2; EtOAc/hexane, 40:60) gave the title compound as a pale yellow gum. Recrystallaisation from MeOH/ isopropanol gave the title compound as pale yellow needles (5.44g, 66%) m.p, 110-111°. δH (DMSO-d^6, 390K,) 7.94-7.86 (4H, m, ArH(CO)$_2$),7.37 (4H, s,ArH), 4.78 (1H, dd, *J* 10.0, 5.4Hz, CHα), 3.71 (3H, s, CO_2Me), 3.29 (1H, dd, *J* 14.4, 5.4Hz, C$\underline{H}_A$H$_B$Ar), 3.11 (1H, dd, *J* 14.4, 10.0Hz, CH$_A\underline{H}_B$Ar), 2.72 (3H, s,NMe) and 1.36 (9H, s, ^{t}Bu); m/z (ESI, 60V) 461 (MNa$^+$).

INERMEDIATE 50

N-Boc-*N*-methyl-*L*-4-amino-*L*-phenylalanine methyl ester

Hydrazine monohydrate (366μl, 7.54mmol) was added to Intermediate 49 (3.00g, 6.85mmol) in absolute EtOH (70ml). The mixture was stirred overnight at room temperature then refluxed for 4h. After cooling to room temperature, the solid was filtered off and the filtrate evaporated *in vacuo*. DCM was added to the residue, the solid filtered off and the filtrate evaporated *in vacuo*. Column chromatography (SiO_2, EtOAc/hexane, 50:50) gave the title compound (2.04g, 97%) as a colourless oil. δH (DMSO-d^6, 390K) 6.86 (2H, d, *J* 8.4Hz, ArH), 6.53 (2H, d,*J* 8.4Hz,ArH), 4.59 (1H, dd, *J* 9.9, 5.5Hz, CHα), 4.45 (2H, br s, $ArNH_2$), 3.66 (3H, s, CO_2Me), 3.04 (1H, dd, *J* 14.4, 5.5Hz, CH$_A\underline{H}_B$Ar), 2.86 (1H, dd, *J* 14.4, 9.9Hz, CH$_A\underline{H}_B$Ar), 2.67 (3H, s, NMe) and 1.35 (9H, s,^{t}Bu); m/z (ESI, 60V) 331 (MNa$^+$).

INTERMEDIATE 51

***N*-Boc-*N*-methyl-*N'*-(3,5-dichloro-isonicotinoyl)-*L*-4-amino phenylalanine methyl ester**

A solution of 3,5-dichloro-isonicotinoyl chloride (1.53g, 7.29mmol) in THF (30ml) was added to a solution of Intermediate 50 (2.04g, 6.62mmol) and NMM (800μl, 7.29mmol) in THF (40ml) at 0°. The mixture was stirred overnight at room temperature and the bulk of the THF removed *in vacuo*. The residue was dissolved in DCM (200ml) and washed with dilute HCl (50ml) and saturated $NaHCO_3$ (50ml), dried (Na_2SO_4) and evaporated *in vacuo*. Column chromatography (SiO_2, MeOH/CH_2Cl_2 5:95 to 7:93) gave a white foam. Recrystallisation from EtOAc gave the title compound (2.53g, 80%) as small white crystals m.p. 167-168°. δH (DMSO-d^6, 390K) 10.38 (1H, br s, CONH), 8.67 (2H, s, PyrH), 7.54 (2H, br d, *J* 7.4Hz, ArH), 7.22 (2H, d, *J* 8.4Hz, ArH), 4.71 (1H, dd, *J* 9.9, 5.4Hz, CHα), 3.70 (3H, s, CO_2Me), 3.21 (1H, dd, *J* 14.4, 5.4Hz, $C\underline{H}_AH_BAr$), 3.02 (1H, dd, *J* 14.4, 10.0Hz, $CH_A\underline{H}_BAr$), 2.70 (3H, s, NMe) and 1.38 (9H, s,^{t}Bu); m/z (ESI, 60V) 504 (MNa^+).

INTERMEDIATE 52

2-Phenyl-*D*-1,3-thiazolidine-4-carboxylic acid

A solution of *D*-cysteine (5g, 28.5mmol) in pyridine (50ml) was treated with benzaldehyde (4.61ml, 45.4mmol) and stirred at 50° for 4h. The mixture was concentrated *in vacuo* and triturated with MeOH to give the title compound as a white solid (4.1g, 69%) (55:45 mixture of diastereoisomers) δH (DMSO-d^6) 7.39 (5H, m), 5.68 (s) and 5.51 (s) together (1H, NCH(Ph)S), 4.24 (t, *J* 4.6Hz) and 3.91 (dd, *J* 8.4, 7.4Hz) together (1H, CHα), 3.39 (1H, m, $C\underline{H}_AH_BS$) and 3.17 (1H, m, $CH_A\underline{H}_BS$).

INTERMEDIATE 53

***N*-Acetyl-2-phenyl-*D*-1,3-thiazolidine-4-carboxylic acid**

A suspension of Intermediate 52 (3.6g, 17.2mmol) in DMF (50ml) was treated dropwise with acetic anhydride (1.8ml., 18.9mmol) and stirred for 3h at room temperature. The reaction was concentrated *in vacuo* to give a solid that was recrystallised from EtOAc/Et_2O to give the title compound as a single diastereomer (3.30g, 76%) δH (DMSO-d^6, 390K) 7.64 (2H, d, *J* 7.1Hz, Ar-H), 7.32 (3H, m, Ar-H), 6.31 (1H, s, NCH(Ph)S), 4.97 (1H, t, *J*

6,2Hz, CHα), 3.44 (1H, dd, J 11.8, 6.8 Hz, CHC$H_A$$H_B$S), 3.26 (1H, dd, J 11.8, 5.9Hz, CHC$H_A$$H_B$S) and 1.94(3H, s, COMe). m/z (ESI, 60V) 252 (MH^+).

INTERMEDIATE 54

5-Phenyl-1,3-thiazolidine-4-carboxylic acid

A mixture of β-phenyl-DL-cysteine hydrochloride [HT Nagasawa *et al*, J. Med. Chem (1987) 30, 1373] (1.32g, 5.65mmol) in acetic acid (11ml) and formaldehyde (37wt% aqueous solution, 0.43ml) was heated to 80° to give a cloudy solution that was cooled to 30° and stirred for 2.5h, then stood at room temperature for 16h. The white precipitate was collected by filtration, washed with Et_2O and dried *in vacuo* to give the title compound (1.04g, 88%). δH (DMSO-d^6) 7.57-7.54 (2H, m, Ar-H), 7.40-7.29 (3H, m, Ar-H), 4.90 (1H, d, CHα-Thiopro), 4.59 (2H, d, J 9.3Hz, NCH_2S), 4.46 (1H, d, J 9.8Hz, CHPh). m/z (ESI, 60V) 210 (MH^+).

INTERMEDIATE 55

***N*-Acetyl-5-phenyl-1,3-thiazolidine-4-carboxylic acid**

Acetic anhydride (0.27g, 0.25ml, 2.6mmol) was added to a solution of Intermediate 54 (0.50g, 2.4mmol) in NMM (0.30g, 0.33ml, 3.0mmol) and DMF (10ml) and stirred for 7h at room temperature. The solvent was removed *in vacuo*, the residue partitioned between DCM and 5% HCl, the organic layer dried ($MgSO_4$) and concentrated *in vacuo* to give a solid that was recrystallised from EtOAc to afford the title compound as a white solid (0.29g, 48%) δH ($CDCl_3$) (two diastereomeric species observed) 7.38-7.26 (5H, m, Ar-H), 5.19 (d, J 3.8Hz) and 5.08 (d, J 9.6Hz) togther (1H, CHα-thiopro), 4.87 (d, J 3.8Hz) and 4.60 (d, J 9.6Hz) together (1H, CHPh), 4.74 (2H, s, NCH_2S), 2.22 (s) and 2.01 (s) together (3H, COMe).

INTERMEDIATE 56

1-Thia-3-azaspiro[4.4]nonane-4-carboxylic acid

A mixture of β,β-tetramethylene-DL-cysteine (1.09g, 5.15mmol); [H. T. Nagasawa *et al*, *ibid*] in acetic acid (10ml) and formaldehyde (37% aqueous solution, 0.39ml) was heated to 80°, cooled to 30° when solution had occurred then stirred at this temperture for 1h. The reaction was concentrated *in vacuo* to give the title compound as a white solid that was

used without further purification (0.72g, 75%). δH (DMSO-d^6) 4.44 (1H, s, CHα), 4.36 (2H, dd, J 13.6, 9.9Hz, NCH_2S) and 2.33-1.69 (8H, m, CH_2).

INTERMEDIATE 57

***N*-Acetyl-1-thia-3-azaspiro[4.4]nonane carboxylic acid**

A solution of Intermediate 56 (300mg, 1.60mmol) in DMF (15ml) and acetic anhydride (172mg, 1.69mmol) was stirred overnight at room temperature, concentrated *in vacuo* and partitioned between water (25ml) and DCM (25ml). The organic fraction was dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound as a brown oil (0.31g, 85%) which was used without further purification. δH ($CDCl_3$) 4.68 (3H, m, CHα and NCH_2S), 2.19 (3H, s, COMe) and 2.17-1.71 (8H,m).

INERMEDIATE 58

3,5-Dichloro-4-hydroxymethyl-pyridine

A solution of 3,5-dichloropyridine-4-carboxaldehyde (1.34g, 7.6mmol) in MeOH (10ml) was treated with $NaBH_4$ (0.29g, 7.6mmol) and stirred at room temperature for 2h. The reaction was quenched with water (5ml) and concentrated *in vacuo*. The residue was partitioned between EtOAc (20ml) and 10% HCl (10ml). The aqueous layer was extracted with EtOAc and the combined organic extracts, washed with 10% $NaHCO_3$ solution, dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound as a white solid (1.05g, 78%). δH ($CDCl_3$) 8.52 (2H, s, pyr-H), 4.94 (2H, br s, CH_2OH) and 2.28 (1H, br s, OH).

INTERMEDIATE 59

3,5-Dichloroisonicotinyl bromide

A solution of Intermediate 58 (0.50g, 2.80mmol) in DCM (10ml) was treated with thionyl bromide (3.51g, 1.32ml, 16.9mmol) and heated to reflux for 3h. The reaction was quenched with 10% $NaHCO_3$ solution (10ml) and extracted wth DCM (25ml). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound as a yellow oil that solidified on standing (0.65g, 96%) and was used without further purification. δH ($CDCl_3$) 8.50 (2H, s, pyr-H), 4.63 (2H, s, CH_2Br). m/z (ESI, 60V) 242 (MH^+).

INTERMEDIATE 60

N-Acetyl-D-thioproline-(O-3,5-dichloroisonicotinoyl)-L-tyrosine methyl ester

To a slurry of NaH (88mg, 2.2mmol, 60% dispersion) in THF (4ml) was added a solution of *N*-acetyl-*D*-thioproline-*L*-tyrosine methyl ester (0.70g, 2.0mmol) in DMF (6ml). The reaction was stirred for 20 min at room temperature then a solution of Intermediate 59 (0.65g, 2.7mmol) in THF (6ml) was added and the reaction stirred for 16h, quenched with water (5ml) and concentrated *in vacuo*. The residue was partitioned between water (20ml) and DCM (20ml), the organic layer dried ($MgSO_4$) and concentrated *in vacuo* to give an oil that was purified by chromatography (SiO_2; EtOAc) to give the title compound as a white solid (0.45g, 44%). δH ($CDCl_3$) 8.55 (2H, s, pyr-H), 7.09 (2H, d, J 8.5Hz, Ar-H), 6.93 (2H, d, J 8.5Hz, Ar-H), 5.22 (2H, s, OCH_2), 5.04 (1H, m, CHα-Thiopro), 4.80 (1H, m, CHα-tyr), 4.59-4.40 (2H, m, NCH_2S), 3.73 (3H, s, CO_2Me), 3.47-3.03 (4H, m, $CHC\underline{H_2}Ar$ + $CHC\underline{H_2}S$) and 1.73 (3H, s, COMe). m/z (ESI, 60V) 512 (MH^+).

INTERMEDIATE 61

N-Acetyl-D-thioproline-(N'-benzenesulphonyl)-L-4-aminophenyl alanine methyl ester

A solution of Intermediate 5 (0.50g, 1.71mmol) in THF (10ml) and triethylamine (0.21g, 0.29ml, 2.05mmol) was treated with benzene sulphonyl chloride (0.30g, 0.22ml, 1.71mmol) and stirred at room temperature for 16h. The mixture was partitioned between EtOAc (20ml) and water (20ml), the organic layer separated and washed with 10% $NaHCO_3$ solution (20ml), 10% HCl (10ml), and brine (20ml), dried ($MgSO_4$) and evaporated *in vacuo* to give a foam that was purified by chromatography (SiO_2; 1:99 AcOH/EtOAc) to give the title compound as a white foam (0.63g, 80%). δH ($CDCl_3$), (2 rotamers observed) 7.75 (3H, m, Ar-H + NH), 7.54-7.40 (3H, m, Ar-H), 7.00 (4H, m, Ar-H), 5.00 (m) and 4.79-4.65 (m) and 4.56 (d, J 8.8Hz) and 4.45 (d, J 8.8Hz) together (4H, 2 x CHα and NCH_2S), 3.73 and 3.66 (together 3H, s, CO_2Me), 3.35-2.94 (4H, m, $CH\alpha C\underline{H_2}Ar$ and $CH\alpha C\underline{H_2}S$), 2.09 and 2.05 (together 3H, s, COMe).

INTERMEDIATE 62

***N*-Acetyl-*D*-thioproline-4-(*N'*-isobutyloxycarbonyl)amino-L-phenylalanine methyl ester**

To a solution of Intermediate 5 (351mg, 1.0mmol) in DCM (10ml) cooled to 0° was added NMM (121µl, 1.1mmol). After 15min isobutylchloroformate (156µl, 1.2mmol) was added dropwise. The reaction mixture was stirred for a further 15min at 0°, diluted with DCM (10ml) and then washed with aqueous HCl (1M, 10ml), saturated aqueous $NaHCO_3$ (10ml) and brine (10ml), dried (Na_2SO_4) and evaporated under reduced pressure. Purification of the residue by column chromatography (SiO_2; EtOAc/DCM,1:1) gave the title compound as a white foam (400mg, 89%). δH ($CDCl_3$) 7.48-6.82 (6H, m, ArH and 2 x NH), 5.00- 4.30 (4H, m, $NC\underline{H}_2S$ and 2 x α-CH), 3.87 (2H, d, *J* 6.7Hz, $OC\underline{H}_2$), 3.69 (s) and 3.64 (s) together (3H, $CO_2C\underline{H}_3$), 3.36-2.87 (4H, m, $C\underline{H}_2Ar$ and $SC\underline{H}_2CH$), 2.10 (s) and 1.81 (s) together (3H, $COC\underline{H}_3$), 1.90 (1H, quin, *J* 6.7Hz, $CH_2C\underline{H}(CH_3)_2$) and 0.89 (6H, d, *J* 6.7Hz, $CH(C\underline{H}_3)_2$); *m/z* (ESI, 60V) 452 (MH^+).

INTERMEDIATE 63

***N*-Acetyl-*D*-thioproline-4-(methylthioureido)-*L*-phenylalanine methyl ester**

A solution of Intermediate 5 (351mg, 1.0mmol) ad methyl isothiocyanate (73mg, 1.0mmol) in Et_2O (10ml) and EtOH (10ml) was refluxed for 18h. The solvents were removed under reduced pressure and the cream foam obtained purified by column chromatography (SiO_2; MeOH/DCM 5:95) to give the title compound as a white foam (401mg, 94%). δH ($CDCl_3$) 8.47 (s) and 8.21 (s) together (1H, NH),7.17-6.48 (6H, m, ArH and 2 x NH), 4.88-4.45 (4H, m, $NC\underline{H}_2S$ and 2 x α-CH), 3.73 (s) and 3.69 (s) together (3H, $CO_2C\underline{H}_3$), 3.33-2.92 (7H, m, CH_2Ar, $SC\underline{H}_2CH$ and $CSNHC\underline{H}_3$) and 2.02 (3H, s, $COC\underline{H}_3$); *m/z* (ESI, 60V) 425 (MH^+).

INTERMEDIATE 64

***N*-Acetyl-*D*-thioproline-4-(*t*-butylureido)-*L*-phenylalanine methyl ester**

To a solution of Intermediate 5 (351mg, 1.0mmol) in acetonitrile (10ml) was added *t*-butylisocyanate (113µl, 1.0mmol). The reaction mixture was heated to reflux for 24h. The solvent was then removed and the residue

obtained purified by column chromatography (SiO_2; DCM/MeOH, 96:4) to give the title compound as a colourless oil (320mg, 71%). δH (DMSO-d^6) 8.55 (d, J 8.0Hz) and 8.26 (d, J 8.2Hz) together (1H, NH), 8.14 (1H, s, NH), 7.25-6.99 (4H, m,ArH), 5.91 (1H, s, NH), 4.82-4.19 (4H, m, SCH_2N and 2 x α-CH), 3.62 (s) and 3.61 (s) together (3H, CO_2Me), 3.49-2.72 (4H, m, CH_2Ar and SCH_2CH), 2.08 (s) and 2.05 (s) and 1.85 (s) together (3H, $COCH_3$) and 1.27 (9H, s, $C(CH_3)_3$); m/z (ESI, 60V) 451 (MH^+).

INTERMEDIATE 65

N-Acetyl-*D*-thioproline-4-(isopropylureido)-*L*-phenylalanine methyl ester

To a solution of Intermediate 5 (351mg, 1.0mmol) in DCM (10ml) was added isopropylisocyanate (118μl, 1.0mmol). The solution was stirred overnight at room temperature. The resulting white precipitate was collected and washed with DCM and dried to give the title compound (150mg, 35%). δH (DMSO-d^6) 8.55 (d, J 8.1Hz) and 8.26 (d, J 7.9Hz) together (1H, NH), 8.19 (1H, s, NH), 7.32-7.20 (2H, m, ArH), 7.10-6.99 (2H, m, ArH), 5.92 (1H, d, J 7.4Hz, NH), 4.82-4.20 (4H, m, NCH_2S and 2 x CHα-H), 3.80-3.68 (1H, m, $CH(CH_3)_2$), 3.62 (s) and 3.61 (s) together (3H, CO_2Me), 3.25-2.75 (4H, m, CH_2Ar and SCH_2CH), 2.05 (s) and 1.84 (s);together (3H, $COCH_3$) and 1.08 (6H, d, J 6.5Hz, $CH(CH_3)_2$); m/z (ESI, 60V) 437(MH^+).

INTERMEDIATE 66

Methyl 2-azido-3-(4-[2-hydroxyhexafluoroisopropyl]phenyl)prop-2-enoate

To a solution of 4-(2-hydroxyhexafluoroisopropyl)benzaldehyde (1.0g, 3.68mmol) and methyl α-azidoacetate (4.23g, 36.8mmol) in MeOH (50ml) cooled to -78° was added a methanolic sodium methoxide solution (0.5M, 58.8ml, 29.4mmol). The reaction mixture was allowed to warm slowly to room temperature and left stirring ovenight. Saturated brine (100ml) was then added and the solution thoroughly extracted with Et_2O. The combined organics were dried (Na_2SO_4) and evaporated under reduced pressure. The solid obtained was triturated with hexane:chloroform and the solution obtained reduced *in vacuo* to leave the title compound as a pale yellow solid (840mg, 62%) δH ($CDCl_3$) 7.88 (2H, d, J 8.5Hz, ArH),

7.73 (2H, d, J 8.5Hz, ArH), 6.90 (1H, s, C=CH) and 3.93 (3H, s, CO_2Me); m/z (ESI, 60V) 342 (MH^+-N_2).

INTERMEDIATE 67

4-(2-Hydroxyhexafluoroisopropyl)-*DL*-phenylalanine methyl ester

A solution of Intermediate 66 (840mg, 2.27mmol) in MeOH (50ml) was degassed thoroughly. Palladium on activated carbon (140mg) was added and the reaction placed under a hydrogen atomosphere (H_2 balloon). The solution was stirred rapidly overnight. DCM (5ml) was added and the catalyst removed by filtration through Celite®. Solvent was evaporated under reduced pressure to give the title compound (600mg, 77%). δH ($CDCl_3$) 7.66 (2H, d, J 8.2Hz, ArH), 7.22 (2H, d, J 8.2Hz, ArH), 4.05 (2H, br s, NH_2) 3.76 (1H, dd, J 6.3, 6.3Hz, CHα), 3.67 (3H, s,CO_2Me), 3.10 (1H, dd, J 13.8, 5.5Hz, $C\underline{H}_AH_B$) and 2.98 (1H, dd, J 13.8 and 7.1Hz, $CH_A\underline{H}_B$); m/z (ESI, 60V) 346 (MH^+).

INTERMEDIATE 68

Methyl 4-{[(2,6-dichlorophenyl)sulphonyl]methyl}benzoate

2,6-Dichlorobenzenesulphonylchloride (1g, 4.07mmol) was added to a solution of sodium sulphite (1.02g, 8.14mmol) in water (15ml). The solution was made basic with the addition of 10% sodium hydroxide solution. The solution was then heated briefly and then cooled and any remaining solids removed by filtration. The solution was then acidified by the addition of 50% sulphuric acid and the resulting white precipitate collected by filtration and dried to give the sulphinic acid (0.86g, 4.07mmol). The acid (0.86g) was then dissolved in acetonitrile (6ml) and DBU (6.2ml, 4.07mmol) followed by the addition of methyl 4-(bromomethyl) benzoate (1.03g, 4.48mmol). The reaction mixture was stirred overnight at room temperature. Water (50ml) was then added and the mixture extracted with DCM (3 x 25ml). The combined organics were dried (Na_2SO_4) and evaporated under reduced pressure. Purification by column chromatography (SiO_2; DCM) gave the title compound as a white solid (300mg, 21%). δH ($CDCl_3$) 7.99-7.89 (2H, m, ArH), 7.43-7.28 (5H, m,ArH), 4.69 (2H, s,CH_2) and 3.87 (3H, s,CO_2Me); m/z (ESI, 60V) 359 (MH^+).

INTERMEDIATE 69

4-{[(2,6-Dichlorophenyl)sulphonyl]methyl}benzyl alcohol

Intermediate 68 (300mg, 0.83mmol) was dissolved in THF (5ml). Lithium aluminium hydride (1M inTHF, 0.83ml, 0.83mmol) was added dropwise. The resulting orange solution was stirred for 1h at room temperature and then quenched with the dropwise addition of water (15ml). The mixture was extracted with DCM (3x25ml) and the combined organics dried (Na_2SO_4), filtered through a pad of Celite® and evaporated under reduced pressure to give the title compound as a colourless oil (284mg, 100%) δH ($CDCl_3$) 7.40-7.20 (7H, m, ArH), 4.72-4.60 (4H, m, CH_2 x 2) and 2.18 (1H, br s, OH); m/z (ESI, 60V) 348 (MNH_4^+).

INTERMEDIATE 70

4-{[(2,6-Dichlorophenyl)sulphonyl]methyl}benzyl bromide

Intermediate 69 (200mg, 0.58mmol) was dissolved in toluene (5ml) and thionyl bromide (0.5ml) was added. The resulting reaction mixture was stirred for 3h. The volatiles were removed under reduced pressure and the residue azeotroped with toluene (x 2). Purification by column chromatography (SiO_2; DCM/Hexane 1:1) gave the title compound as a colourless oil (180mg, 79%) δH ($CDCl_3$) 7.41-7.20 (7H, m, ArH), 4.65 (2H, s,CH_2) and 4.43 (2H, s,CH_2) m/z (ESI, 60V) 412 (MNH_4^+) .

INTERMEDIATE 71

Ethyl 2 amino-3-(4-{[(2,6-dichlorophenyl)sulphonyl]methyl} propanoate

LDA (2M in heptane/THF/ethylbenzene, 2.10ml, 4.19mmol) was added to a stirred solution of *N*-(diphenylmethylene)glycine ether ester (1.07g, 3.99mmol) in THF (40ml) cooled to -78°. The reaction mixture was stirred at this temperature for 40min. A solution of Intermediate 70 (1.5g, 3.81mmol) in THF (20ml) was then added dropwise. The reaction mixture was stirred for a further hour at -78°, then warmed slowly to ambient temperature, and quenched with saturated aqueous NH_4Cl (50ml). Ethyl acetate (75ml) was added and the organic phase separated. The aqueous layer was extracted with EtOAc (x 2) and the combined organics dried (Na_2SO_4) and evaporated under reduced pressure. The residue was then dissolved in EtOH (50ml) and 1M HCl (20ml) was added. After 30min the

solvents were removed and the resulting residue partitioned between EtOAc (100ml) and saturated aqueous $NaHCO_3$. The phases were separated and the aqueous phase extracted with EtOAc (2x). The combined organics were dried (Na_2SO_4) and evaporated under reduced pressure. The resulting oil was purified by column chromatography (SiO_2; EtOAc) to give the title compound as a colourless oil (1.00g, 60%) δH ($CDCl_3$) 7.61 (2H, d, J 8.2Hz, ArH), 7.27 (2H, d, J 8.2Hz, ArH), 7.22-7.19 (2H, m, $ArCl_2H$), 7.12 (1H, dd, J 9.2, 6.5Hz,$ArCl_2H$), 4.73 (2H, s, $SO_2C\underline{H_2}$), 4.10 (2H, q, J 7.1Hz, $C\underline{H_2}CH_3$), 3.65 (1H, dd, J 7.5, 5.5Hz, CH), 3.06 (1H, dd, J 13.5, 5.5Hz, $C\underline{H_A}H_B$), 2.87 (1H, dd, J 13.5, 7.5Hz, $CH_A\underline{H_B}$), 1.45 (2H, br s, $N\underline{H_2}$) and 1.16 (3H, t, J 7.1Hz, $CH_2C\underline{H_3}$); m/z (ESI, 60V) 416 (MH^+).

INTERMEDIATE 72

Ethyl 2-amino-3-{4-[(2,6-dichlorobenzyl)sulphonyl]phenyl}propanoate

The title compound was prepared in a similar manner to Intermediate 71 from 4-[(2,6-dichlorobenzy)sulphonyl]benzyl bromide *N*-(diphenylmethylene)glycine ethyl ester. δH ($CDCl_3$) 7.38-7.29 (3H, m, ArH), 7.15-7.06 (4H, m, ArH), 4.60 (2H, s,$C\underline{H_2}SO_2$), 4.11 (2H, q, J 7.1Hz, $C\underline{H_2}CH_3$), 3.63 (1H, dd, J 7.7, 5.3Hz, CH), 3.01 (1H, dd, J 13.5, 5.3Hz, $C\underline{H_A}H_B$), 2.80 (1H, dd, J 13.5, 7.7Hz, $CH_A\underline{H_B}$), 1.53 (2H, br sm NH_2) and 1.21 (3H, t, J 7.12Hz, $CH_2C\underline{H_3}$); m/z (ESI, 60V) 416 (MH^+).

EXAMPLE 1

N-(Pyrid-3-ylacetyl)-*D*-thioproline-(*N'*-2,6-dichlorobenzoyl)-*L*-4-aminophenylalanine

A solution of Intermediate 4 (1.06g, 1.08mmol) in dioxane/MeOH (1:1, 60ml) and water (30ml) was treated with lithium hydroxide monohydrate (53.0mg, 1.3mmol) and stirred at room temperature for 1.5h. The reaction was acidified to pH 4.5 with glacial acetic acid to give a precipitate which was isolated by filtration, washed with dilute acetic acid and hexane then dried *in vacuo* to give the title compound as a white solid (0.67g, 65%). δH (DMSO-d^6, 390K) 10.19 (1H, s, CO_2H), 8.43 (2H, m, Ar-H), 7.88 (1H, br s, NH), 7.62-7.41 (6H, m, Ar-H, pyr-H), 7.28 (1H, m, Ar-H), 7.20 (2H, d, J 8.4Hz, Ar-H), 4.94 (1H, dd, J 4.1, 7.4Hz, CH_α-thiopro), 4.86 (1H, d, J

9.2Hz, NC$\underline{H}_A$H$_B$S), 4.55 (1H, m, CH$_\alpha$-Ph), 4.45 (1H, d, $\underline{J}$ 9.2Hz, NCH$_A\underline{H}_B$S), 3.74 (2H, m, CH$_2$pyr) and 3.31-2.96 (4H, m, ArCH$_2$, CHC$\underline{H}_2$S). $\underline{m/z}$ (ESI, 30V) 587 (MH+).

EXAMPLE 2

a) *N*-Acetyl-*D*-thioproline-(*N'*-3,5-dichloroisonicotinoyl)-*L*-4-aminophenylalanine

A solution of Intermediate 7 (120mg, 0.23mmol) in THF (4ml) and water (3ml) was treated with lithium hydroxide monohydrate (14.4mg, 0.34mmol) and stirred for 2h at room temperature. The reaction was acidified to pH1 with 10% hydrochloric acid and the volatiles were removed *in vacuo*. The solid residue was triturated with water, isolated by filtration and washed with water and dried *in vacuo* to give the title compound as an off-white solid (100mg, 85%). δH (DMSO-d^6, 390K) 10.41 (1H, s, NH), 8.68 (2H, s, pyr-H), 7.77 (1H, br s, NH), 7.54 (2H, br d, $\underline{J}$ 7.9Hz, Ar-H), 7.23 (2H, d, $\underline{J}$ 8.4Hz, Ar-H), 4.83 (1H, dd, $\underline{J}$ 4.0, 7.4Hz, CH$_\alpha$-Thiopro), 4.76 (1H, d, $\underline{J}$ 9.2Hz, NC$\underline{H}_A$H$_B$S), 4.54 (1H, dt, $\underline{J}$ 5.4, 8.3Hz, CH$_\alpha$-Ph), 4.38 (1H, d, $\underline{J}$ 9.2Hz, NCH$_A\underline{H}_B$S), 3.25 (1H, dd, $\underline{J}$ 7.4, 11.5Hz, CHC$\underline{H}_A$H$_B$S), 3.15 (1H, dd, $\underline{J}$ 5.4, 14.1Hz, ArC$\underline{H}_A$H$_B$), 3.04-2.92 (2H, m, CHCH$_A\underline{H}_B$S and ArCH$_A\underline{H}_B$) and 1.99 (3H, s, COCH$_3$). $\underline{m/z}$ (ESI, 70V) 511, (MH+).

The following compounds were prepared in a similar manner to the compound of Example 2a):

b) *N*-Acetyl-*D*-thioproline-*O*-[2-(4-methoxythiophenoxy)pyrimidin-4-yl]-*L*-tyrosine

from Intermediate 47: δH (DMSO-d^6, 400K) 8.39 (1H, d, $\underline{J}$ 5.6Hz, PyH), 7.75 (1H, br d, CONH), 7.41 (2H, d, $\underline{J}$ 8.9Hz, ArH), 7.21 (2H, d, $\underline{J}$ 8.6Hz, ArH), 7.00 (2H, d, $\underline{J}$ 8.6Hz, ArH), 6.92 (2H, d, $\underline{J}$ 8.9Hz, ArH), 6.64 (1H, d, $\underline{J}$5.6Hz, PyrH), 4.83 (1H, dd, $\underline{J}$ 7.3, 3.9Hz, CHαthiopro), 4.77 (1H, d, $\underline{J}$ 9.2Hz, NC$\underline{H}_A$H$_B$S), 4.57 (1H, dt, $\underline{J}$ 8.3, 5.4Hz, CHαtyr), 4.39 (1H, d, $\underline{J}$ 9.1Hz, NCH$_A\underline{H}_B$S), 3.83 (3H, s, OMe), 3.26 (1H, dd, $\underline{J}$ 11.4, 7.4Hz, CHC$\underline{H}_A$H$_B$S), 3.18 (1H, dd, $\underline{J}$ 14.1, 5.4Hz, CHC$\underline{H}_A$H$_B$Ar), 3.04-2.97 (2H, m, CHCH$_A\underline{H}_B$S + CHCH$_A\underline{H}_B$Ar) and 1.99 (3H, s,COCH$_3$) (acid signal not observed at 400K); $\underline{m/z}$ (ESI, 30V) 555 (MH+).

c) *N*-Acetyl-*D*-thioproline-*O*-(2-chloropyrimidin-4-yl)-*L*-tyrosine

from Intermediate 46 as a white solid δH (DMSO-d^6, 400K) 8.56 (1H, d, J 5.7Hz, PyH), 7.72 (1H, br s, CONH), 7.33 (2H, d, J 8.7Hz, ArH), 7.13 (2H, d, J 8.7Hz, ArH), 6.98 (1H, d, J 5.7Hz, PyH). 4.83 (1H, dd, J 7.4, 4.0Hz,CHαthiopro), 4.77 (1H, d, J 9.2Hz, NCH_AH_BS), 4.56 (1H, br m, CHαtyr), 4.38 (1H, d, J 9.3Hz, NCH_AH_BS), 3.29-3.18 (2H, m, 2 x $CHCH_AH_B$), 3.07-3.00 (2H, m,2 x $CHCH_AH_B$) and 1.99 (3H, s, $COCH_3$) (acid signal not observed at 400K); m/z (ESI, 15V) 451 (MH^+).

d) *N*-(Pyrid-3-ylacetyl)-*D*-thioproline-*O*-(2,4,6-trichlorobenzyl)-*L*-tyrosine

from Intermediate 43 as an off-white solid. δH (DMSO-d^6, 400K) 8.51 (2H, br s PyH), 7.8 (1H, br d, CONH), 7.65 (1H,d, PyH), 7.61 (2H, s,Cl_3ArH), 7.3 (1H, dd, PyH), 7.16 (2H, d, J 8.4Hz, ArH), 6.93 (2H, d, J 8.5Hz,ArH), 5.22 (2H, s, OCH_2Ar), 4.93 (1H, dd, J 7.4,4.0Hz, CHαthiopro), 4.86 (1H, d, J 9.2Hz, NCH_AH_BS),4.55 (1H, dt,CHαtyr), 4.44 (1H, d, J 9.3Hz, NCH_AH_BS), 3.73 (2H, m, $COCH_2Py$) and 3.09-2.94 (4H, m, 2x $CHCH_2$) (acid proton not observed at 400K); m/z (ESI) 608 (MH^+).

e) *N*-Acetyl-*D*-thioproline-4-(2,6-dichlorophenylacetylene)-*L*-phenylalanine

from Intermediate 39 as a white solid. δH (DMSO-d^6, 390K) 7.83 (1H, br d, CONH), 7.55-7.48 (3H, m, ArH + Cl_2ArH), 7.40 (1H,dd, J 8.9, 7.3Hz, Cl_2ArH), 7.32 (2H, d, J 8.3Hz, ArH), 4.83 (1H, dd, J 7.3, 3.9Hz, CHαthiopro), 4.77 (1H, d, J 9.2Hz, NCH_AH_BS), 4.57 (1H,dt, J 8.4, 5.3Hz, CHαPh), 4.38 ((1H, d, J 9.1Hz, NCH_AH_BS), 3.26 (1H, dd, J 11.5, 7.4Hz, $CHCH_AH_BS$), 3.20 (1H, dd, J 14.1, 5.3Hz, $CHCH_AH_BAr$), 3.08-2.99 (2H, m, $CHCH_AH_BS$ + $CHCH_AH_BAr$) and 1.99 (3H, s, $COCH_3$) (acid proton not observed at 390K); m/z (ESI, 15V 491 (MH^+).

f) *N*-Acetyl-*D*-thioproline-4-(*N'*-thioacetyl)amino-*L*-phenylalanine

from intermediate 31: δH (DMSO-d^6) (2 rotamers observed) 11.50 (1H, s, CO_2H), 8.46 (d, J 8.3Hz) and 8.19 (d, J 8.3Hz) together (NH), 7.68 (2H, d, J 8.5Hz, ArH), 7.21 (2H, dd, J 8.5, 8.5Hz, ArH), 4.85-4.69 (2H, m, NCH_2S), 4.53-4.19 (2H, m, 2 x αCH), 3.31-2.71 (4H, m, CH_2Ar and SCH_2CH), 2.58

(3H, s,CSC$\underline{H}_3$) and 2.05 (s) and 1.82 (s) together (3H, $COCH_3$); m/z (ESI, 60V) 396 (MH^+).

g) *N*-Acetyl-*D*-thioproline-4-(*N'*-thiobenzoyl)amino-*L*-phenylalanine from the corresponding methyl ester prepared in a similar manner to Intermediate 31: δH (DMSO-d^6) 8.50 (d, J 8.1Hz) and 8.22 (d, J 8.4Hz) together (1H,NH), 7.85-7.72 (4H,m, ArH), 7.56-7.48 (3H, m, ArH), 7.32-7.18 (2H, m, ArH), 4.80-4.65 (2H, m, NC$\underline{H}_2$S), 4.52-4.20 (2H, m, 2 x CHα), 3.24-2.73 (4H, m, C$\underline{H}_2$Ar and SC$\underline{H}_2$CH) and 2.06 (s) and 1.85 (s) together (3H, $COCH_3$); m/z (ESI, 60V) 458 (MH^+).

h) *N*-Acetyl-*D*-thioproline-4-(*t*-butylureido)-*L*-phenylalanine from Intermediate 64: δH (DMSO-d^6) 8.42-8.05 (2H, m,2 x N$\underline{H}$), 7.28-6.99 (4H, m, ArH), 5.92 (1H, s,N$\underline{H}$), 4.83-4.18 (4H, m, NC$\underline{H}_2$S and 2 x α-CH), 3.22-2.21 (4H, m, C$\underline{H}_2$Ar and SC$\underline{H}_2$CH) 2.0(s) and 1.84 (s); together (3H, $COCH_3$) and 1.27 (9H, s, C(C$\underline{H}_3$)$_3$); m/z (ESI, 60V) 437 (MH^+).

i) *N* Acetyl-*D*-thioproline-4-(isopropylureido)-*L*-phenylalanine from Intermediate 65: δH (DMSO d^6) 8.39 (d, J 8.1Hz) and 8.10 (d, J 8.1Hz) together (1H, NH), 8.18 (1H, s,NH),7.31-7.20 (2H, m, ArH), 7.10-6.98 (2H, m, ArH), 5.92 (1H, d, J 7.5Hz, NH), 4.83-4.20 (4H, m, NC$\underline{H}_2$S and 2 x CHα), 3.82-3.68 (1H, m, C$\underline{H}$(CH_3)$_2$), 3.22, 2.72 (4H, m, C_2Ar and SC$\underline{H}_2$CH), 2.05 (s) and 1.84 (s) together (3H, COC$\underline{H}_3$) and 1.08 (6H, d, J 6.5Hz, CH(C$\underline{H}_3$)$_2$); m/z (ESI, 60V) 423 (MH^+).

j) *N*-Acetyl-*D*-thioproline-4-(methylthioureido)-*L*-phenylalanine from Intermediate 63: δH (DMSO-d^6) 9.48 (1H, br s, NH), 8.48 (d, J 8.3Hz) and 8.11 (d, J 8.3Hz) together (1H, NH), 7.60 (1H, br s, NH), 7.35-7.10 (4H, m, ArH), 4.82-4.18 (4H, m, NC$\underline{H}_2$S and 2 x α-CH), 3.40-2.75 (7H, m, CH_2Ar, SC$\underline{H}_2$CH and CSNHC$\underline{H}_3$) and 2.05 (s) and 1.83 (s) together (3H, COC$\underline{H}_3$); m/z (ESI, 60V) 411 (MH^+).

k) *N*-Acetyl-*D*-thioproline-(*O*-3,5-dichloroisonicotinoyl)-*L*-tyrosine from Intermediate 60: δH (DMSO-d^6, 400K) 8.63 (2H, s, pyr-H), 7.55 (1H, br s, NH), 7.16 (2H, AB d, J 8.7Hz, Ar-H), 6.93 (2H, AB d, J 8.7Hz, Ar-H), 5.26 (2H, s, CH_2O), 4.80 (1H, m, CHα-thiopro), 4.77 (1H, d, J 9.2Hz,

NC$\underline{H}_A$$H_B$S), 4.41 (1H, m, CHα–Tyr), 4.36 (1H, d, J 9.2Hz, NC$H_A$$\underline{H}_B$S), 3.23 (1H, dd, J 11.4, 7.4Hz, CHC$\underline{H}_A$$H_B$S), 3.14-2.91 (3H, m, CHC$H_A$$\underline{H}_B$S + CHC$\underline{H}_2$Ar) and 1.97 (3H, s, COMe). m/z (ESI, 60V) 498 (MH^+).

l) *N*-Acetyl-*D*-thioproline-4-(*N'*-isobutyloxycarbonyl)amino-*L*-phenylalanine

from Intermediate 62: δH (DMSO-d^6) 9.50 (1H, s, NH), 8.41 (d, J 8.0Hz) and 8.11 (d, J 8.1Hz; together (1H, NH), 7.39-7.29 (2H, m, ArH), 7.15-7.03 (2H, m, ArH), 4.83-4.19 (4H, m, NC$\underline{H}_2$S and 2 x α-CH), 3.85 (2H, d, J 6.7Hz, OCH_2), 3.22-2.70 (4H, m, C$\underline{H}_2$Ar and SC$\underline{H}_2$CH), 2.05 (s) and 1.83 (s); together (3H, COC$\underline{H}_3$), 1.91 (1H, quin. J 6.7Hz, $CH_2C\underline{H}(CH_3)_2$) and 0.92 (6H, d, J 6.7Hz, $CH_2CH(C\underline{H}_3)_2$); m/z (ESI, 60V) 438 ($MH^+$).

EXAMPLE 3

a) *N*-(Pyrid-3-ylacetyl)-*D*-thioproline-(*O*-2,4,6-trichlorobenzoyl)-*L*-tyrosine

A solution of the methyl esters, Intermediate 11 (0.65g, 1.0mmol) in dioxane/MeOH (1:1, 40ml) and water (20ml) was treated with lithium hydroxide monohydrate (44mg, 1.1mmol). The reaction was stirred at room temperature for 1.5h then glacial acetic acid was added to adjust the pH to 4.5. The solvent was removed *in vacuo* and the residue purified by chromatography [SiO_2; DCM (200), MeOH (20), ethanol (3) and water (2)], to give two products: the title compound (132mg, 21%) and *N*-(pyrid-3-ylacetyl)-*L*-thioproline-(*O*-2,4,6-trichlorobenzoyl)-*L*-tyrosine (55mg), 9%. (*D*-isomer) δH (DMSO-d_6, 390K) 8.42 (2H, m, pyr-H), 7.89 (1H, br s, NH), 7.77 (2H, s, chloro-Ar-H), 7.61 (1H, d, J 7.7Hz, pyr-H), 7.35 (2H, d, J 8.5Hz, Ar-H), 7.28 (1H, m, pyr-H), 7.18 (2H, d, J 8.5Hz, Ar-H), 4.93 (1H, dd, J 4.0, 7.4Hz, CH_α-thio), 4.86 (1H, d, J 9.2Hz, NC$\underline{H}_A$CH_BS), 4.57 (1H, m, CH_α-tyr), 4.46 (1H, d, J 9.2Hz, NC$_A$C$\underline{H}_B$S), 3.72 (2H, m, CH_2-pyr) and 3.31-2.99 (4H, m). m/z (ESI, 15V) 622, (MH^+).

L-isomer (DMSO-d_6, 390K) 8.41 (1H, m, pyr-H), 7.87 (1H, br s, NH), 7.77 (2H, s, chloro-Ar-H), 7.59 (1H, d, J 7.8Hz, pyr-H), 7.37 (2H, d, J 8.6Hz, Ar-H), 7.26 (1H, dd, J 4.9, 7.8Hz, pyr-H), 7.17 (2H, d, J 8.6Hz, Ar-H), 4.93 (1H, dd, J 3.8, 7.4Hz, CH_α thiopro), 4.84 (1H, d, J 9.2Hz, NC$\underline{H}_A$CH_BS), 4.61 (1H, m, CH_αtyr), 4.45 (1H, d, J 9.2Hz, NCH_AC$\underline{H}_B$S), 3.69 (2H, m,

CH_2-pyr) and 3.01-2.98 (4H, m, Ar-CH_2 and CHC<u>H</u>$_2$S). m/z (ESI, 15V) 622 (MH^+).

The following compounds were prepared in a similar manner from the corresponding methyl ester. Each ester starting material was prepared from intermediate 10 and either 2,6-dimethoxybenzoyl chloride or 2,4-dimethoxybenzoyl chloride in a similar manner to Intermediate 11:

b) *N*-(Pyrid-3-acetyl)-*L*-thioproline-(*O*-2,6-dimethoxybenzoyl)-*L*-tyrosine

δH (DMSO-d^6, 390K) 8.43 (2H, m, pyr-H), 7.77 (1H, br s, NH), 7.60 (1H, m, pyr-H), 7.40 (1H, t, J 8.4Hz Ar(OMe)$_2$H), 7.29 (3H, m, Ar (OMe)$_2$H and pyr-H), 7.06 (2H, ABd, J 8.5Hz, Ar-H), 6.77 (2H, ABd, J 8.5Hz, Ar-H), 4.95 (1H, dd, J 7.4, 3.8Hz, CHα-thio), 4.85 (1H, d, J 9.3Hz, NCH_AH_BS), 4.58 (1H, m, CHα-tyr), 4.45 (1H, d, J 9.3Hz, NCH_AH_BS), 3.87 (6H, s OMe), 3.72 (2H, m, CH_2CO), 3.33 (1H, dd, J 11.6, 7.4Hz, CHCH_AH_BS), 3.18 (1H, dd, J 14.2, 5.4Hz, CH_AH_BAr), 3.15 (1H, dd, J 11.6, 3.8Hz, CHCH_AH_BS) and 3.04 (1H, dd, J 14.2, 8.0Hz, CH_AH_BAr). m/z (ES+, 70V), 580 (MH^+).

c) *N*-(Pyrid-3-acetyl)-*D*–thioproline-(*O*-2,4-dimethoxybenzoyl)-*L*-tyrosine

δH (DMSO-d^6, 390K) 8.43 (2H, m, pyr-H), 7.83 (1H, br s, NH), 7.62 (1H, m, pyr-H), 7.41 (1H, t, J 8.4Hz, Ar(OMe)$_2$-H), 7.30 (3H, m, Ar(OMe)$_2$-H, pyr-H), 7.09 (2H, ABd, J 8.5Hz, Ar-H), 6.77 (2H, ABd, J 8.5Hz, Ar-H), 4.95 (1H, dd, J 7.4, 4.0Hz, CHα-Thiopro), 4.87 (1H, d, J 9.2Hz, NCH_AH_BS), 4.57 (1H, m, CHα-tyr), 4.46 (1H, d, J 9.2Hz, NCH_AH_BS), 3.87 (6H, s, OMe), 3.79-3.67 (2H, m, CH_2O), 3.29 (1H, dd, J 11.6, 7.4Hz, CHCH_AH_BS), 3.06-3.00 (2H, m, CHCH_AH_BS) and CHCH_AH_BAr, m/z (ES+, 70V), 580 (MH^+).

EXAMPLE 4

N-Acetyl-*D*-thioproline-(*O*-pyrimidin-2-yl)-*L*-tyrosine

Lithium hydroxide (51mg, 1.2mmol) was added to a solution of Intermediate 14 (470mg, 1.09mmol) in a mixture of THF (10ml) and water (10ml). The mixture was stirred at room temperature for 30min, then the THF was evaporated *in vacuo*. The aqueous residue was acidified (1M, hydrochloric acid) and the precipitate obtained filtered off, washed with

water and dried to give the title compound as a white powdery solid (269mg, 59%). δH (DMSO-d^6, 400K) 8.60 (2H, d, J 4.8Hz, 2 x HetArH), 7.74 ((1H, br d, CONH), 7.26 (2H, d, J 8.7Hz, CH_2ArH), 7.20 (1H, t, J 4.7Hz, HetArH), 7.08 (2H, d, J 8.7Hz, CH_2ArH), 4.83 (1H, dd, J 4.1, 7.3Hz, CHαthiopro), 4.78 (1H, d, J 9.2Hz, NC$H_A$$H_B$S), 4.57 (1H, dt, J 5.4, 8.3Hz, CHαtyr), 4.38 (1H, d, J 9.2Hz, NCH$_A$$H_B$S), 3.25 (1H, dd, J 7.4, 11.6Hz, CHC$H_A$$H_B$S), 3.18 (1H, dd, J 5.4, 14.1Hz, C$H_A$$H_B$Ar), 3.04-2.97 (2H, m, CHCH$_A$$H_B$S + CH$_A$$H_B$Ar) and 2.00 (3H, s, CH_3CO); m/z (ESI, 27V) 417 (MH$^+$).

EXAMPLE 5

***N*-(Pyrid-3-ylacetyl)-*D*-thioproline-(*O*-2,6-dichlorobenzoyl)-*L*-tyrosine**

Lithium hydroxide monohydrate (6mg, 0.14mmol) was added to an ice-bath cooled solution of Intermediate 15 (100mg, 0.17mmol) in dioxane (4ml), methanol (2ml), and water (3ml). The cooling bath was removed and the reaction mixture stirred at room temperature for 1h. The pH was made slightly acidic by addition of two drops of acetic acid and the solvent removed *in vacuo*. The obtained solid was chromatographed [SiO_2; DCM (002), MeOH (2), ethanol (3), H_2O (2)] which yielded a colourless oil. This was dissolved in a small volume of methanol, diluted with water, and freeze-dried to afford the title compound as a white amorphous solid (60mg, 68%): δH (DMSO-d^6, 400K), 8.45-8.40 (2H, m, pyrH), 7.83 (1H, br s, NH), 7.63-7.52 (4H, m, Ar(Cl)H and pyrH), 7.34 (2H, d, J 8.6Hz, ArH), 7.26 (2H, dd, J 4.7, 7.7Hz, pyrH), 7.17 (1H, d, J 8.6Hz, ArH), 4.94 (1H, dd, J 7.4, 4Hz, CHαthiopro), 4.86 (1H, d, J 9.2Hz, NC$H_A$$H_B$S), 4.58-4.49 (1H, m, CHαtyr), 4.45 (1H, d, J 9.2Hz, NCH$_A$$H_B$S), 3.76 (1H, d, J 16Hz, C$H_A$$H_B$pyr), 3.66 (1H, d, J 16Hz, NCH$_A$$H_B$pyr), 3.28 (1H, dd, J 7.4, 11.6Hz, CHC$H_A$$H_B$S), 3.20 (1H, dd, J 5.5, 14Hz, C$H_A$$H_B$Ar), 3.08-3.01 (2H, m, CHCH$_A$$H_B$S and CH$_A$$H_B$ar); m/z (ESI, 27V) 588 (MH$^+$).

EXAMPLE 6

***N*-Acetyl-*D*-thioproline-(N'-2,6-dichlorobenzoyl)-*L*-4-aminophenyl-alanine**

Intermediate 16 (165mg, 0.31mmol) was treated with a solution of lithium hydroxide monohydrate (16mg, 0.38mmol) in dioxane (2ml), MeOH(2ml), and water (3ml) for 3h at room temperature. The pH was made slightly

acidic with a few drops of acetic acid and the solvent removed *in vacuo*. The residue was treated with water and the obtained solid was collected by filtration with further water washing. The title compound was isolated as a white powder (120mg, 75%) after drying *in vacuo* (50°, overnight): δH (DMSO-d^6, 400K), 10.13 (1H, br s, ArNHCO), 7.69 (1H, br d *J* ~8Hz, NHCO), 7.52 (1H, br d, *J* ~8Hz), 7.52-7.41 (3H, m, Ar(Cl)H), 7.19 (1H, d, *J* 8.4Hz, ArH), 4.84 (1H, dd, *J* 3.9, 7.4Hz, CHα-thiopro), 4.77 (1H, d, *J* 9.2Hz, NCH_AH_BS), 4.54 (1H, ddd, *J* 5.5, 8.1, 8.2Hz, CHα–tyr), 4.38 (1H, d, *J* 9.2Hz, NCH_AH_BS), 3.25 (1H, dd, *J* 7.4, 11.5Hz$CHCH_AH_BS$), 3.12 (1H, dd, *J* 5.5, 14.1Hz, CH_AH_BAr), 3.01 (1H, dd, *J* 3.9, 11.5Hz, $CHCH_AH_BS$), 2.97 (1H, dd, *J* 8.2, 14.1Hz, CH_AH_BAr) and 1.99 (3H, s, $COCH_3$); m/z (ESI, 27V) 510 (MH^+).

EXAMPLE 7

N-(Pyrid-3-ylacetyl)-*D*-thioproline-(*O*-benzyl)-*L*-tyrosine

Intermediate 19 (190mg, 0.37mmol) was treated with a solution of lithium hydroxide monohydrate (19mg, 0.54mmol) in dioxane (2ml), MeOH (2ml) and water (2ml) at room temperature for 2.5h. The pH was made slightly acidic by addition of a few drops of acetic acid and the solvent removed *in vacuo*. The obtained solid was treated with water and collected by filtration with further water washing. After drying *in vacuo* (50°, overnight) the title compound was obtained as a white amorphous solid (105mg, 57%). δH (DMSO-d^6, 400K), 8.46-8.40 (2H, m, pyr H), 7.75 (1H, br d, *J* 6.0Hz, NH), 7.61 (1H, d, *J* 7.9Hz, pyrH), 7.44-7.27 (6H, m, ArH and pyrH), 7.13 (2H, d, *J* 8.6Hz, ArH), 6.89 (2H, d, *J* 8.6Hz, ArH), 5.06 (2H, s, CH_2O), 4.92 (1H, dd, *J* 7.4, 4.0Hz, CH_αthiopro), 4.86 (1H, d, *J* 9.2Hz, NCH_AH_BS), 4.53 (1H, ddd, *J* 8.3, 8.1, 5.5Hz, CH_αtyr), 4.43 (1H, d, *J* 9.2Hz, NCH_AH_BS), 3.75 (1H, d, *J* 16.1Hz, CH_AH_Bpyr), 3.66 (1H, d, *J* 16.1Hz, CH_AH_Bpyr), 3.27 (1H, dd, *J* 11.6, 7.4Hz, $CHCH_AH_BS$), 3.12-2.88 (3H, m, $CHCH_AH_BS$ and (CH_2Ar); m/z (ESI), 506 (MH^+).

EXAMPLE 8

N-Acetyl-*D*-thioproline-(*N'*-3,5-dichlorobenzoyl)-*L*-4-aminophenylalanine

Intermediate 5 was reacted with 3,5-dichlorobenzoyl chloride in a similar manner to that described for Intermediate 16. Subsequent hydrolysis as

described for the compound of Example 2, afforded the title compound as a white powder (925mg). δH (DMSO-d^6) (1:1 mixture of rotamers) 10.36 (1H, s), 8.44 and 8.13 (1H, d, *J* 7.0Hz), 7.97 (2H, d, *J* 1.9Hz), 7.85 (1H, t, *J* 1.9Hz), 7.65 (2H, app.d, *J* 7.0Hz), 7.20 (2H, app.t, *J* 9.0Hz), 4.82-4.75 (1H, m), 4.73 (H, app.t, *J* 8.4Hz), 4.50-4.36 (1H, m), 4.46 (0.5H, d, *J* 8.9Hz), 4.25 (0.5H, d, *J* 8.9Hz), 3.30-2.85 (4H, m's), 2.06 and 1.85 (3H, s); m/z (ESI, 60V) 510 (MH^+).

EXAMPLE 9

***N*-Acetyl-*D*-thioproline-[*N'*-2-fluoro-6-(trifluoromethyl)benzoyl]-*L*-4-aminophenylalanine**

Intermediate 5 was reacted with 2-fluoro-6-(trifluoromethyl)benzoyl chloride in a similar manner to that described for Intermediate 16. Subsequent hydroylsis as described for the compound of Example 2, afforded the title compound as a white powder (650mg). δH (DMSO-d^6, 400K), 10.18 (1H, s), 7.75-7.53 (4H,m), 7.51 (2H, d, *J* 8.4Hz), 7.19 (2H, d, *J* 8.4Hz), 4.83 (1H, dd, *J* 7.3, 3.9Hz), 4.77 (1H, d, *J* 9.2Hz), 4.57-4.50 (1H, m), 4.38 (1H, d, *J* 9.2Hz), 3.25 (1H, dd, *J* 11.6, 7.4Hz), 3.12 (1H, dd, *J* 14.1, 5.3Hz), 3.04 (1H, dd, *J* 11.6, 3.9Hz), 2.98 (1H, dd, *J* 14.1, 8.1Hz) and 1.99 (3H, s); m/z (ESI, 60V) 528 (MH^+).

EXAMPLE 10

***N*-Acetyl-*D*-thioproline-(*N'*-2,4,6-trichlorobenzoyl)-*L*-4-aminophenylalanine**

Intermediate 5 was reacted with 2,4,6-trichlorobenzoyl chloride in a similar manner to that described for Intermediate 16. Subsequent hydrolysis, as described for the compound of Example 2, afforded the title compound as a white powder (950mg). δH (DMSO-d^6, 1:1 mixtures of rotamers), 10.68 (1H,s), 8.46 and 8.15 (1H, d, *J* 8.0Hz), 7.82 (2H, s), 7.55 (2H, approximate d, *J* 7.0Hz), 7.19 (2H, approximate t, *J* 9.0Hz), 4.80-4.68 (2H, m), 4.46 (1H, d, *J* 9.0Hz), 4.46-4.35 (1H,m), 4.23 (1H, d, *J* 9.0Hz), 3.35-2.76 (4H, m), 2.05 and 1.84 (3H, s); m/z (ESI, 60V) 544 (MH^+).

EXAMPLE 11

***N*-Acetyl-*D*-thioproline-(*N'*-2,6-dichlorobenzyl)-L-4-aminophenyl alanine**

Intermediate 21 was hydrolysed and purified in a similar manner to that described for the compound of Example 5. Freeze-drying afforded the title compound as a white amorphous solid (206mg). δH (DMSO-d^6, 390K), 7.62 (1H, br d, J 7.0Hz), 7.44 (2H, app.d, J 7.0Hz), 7.32 (1H, app.t, J 8.0Hz), 6.95 (2H, d, J 8.6Hz), 6.66 (2H, d, J 8.6Hz), 4.81 (1H, dd, J 7.4, 4.0Hz), 4.76 (1H, d, J 9.2Hz), 4.47 (2H, s), 4.46 (2H, m), 4.36 (1H, d, J 9.2Hz),3.24 (1H, dd, J 11.5, 7.4Hz), 3.03-2.95 (2H, m), 2.83 (1H, dd, J 14.1, 8.1Hz) and 1.98 (3H, s); m/z (ESI, 30V) 496 (MH+).

EXAMPLE 12

***N*-Acetyl-*D*-thioproline-(*N'*-acetyl-*N'*-2,6-dichlorobenzyl)-*L*-4-aminophenylalanine**

Intermediate 21 was N-acetylated with acetic anhydride in DCM and subsequently hydrolysed and purified in a similar manner to that described for the compound of Example 5. Freeze-drying afforded the title compound as a white amorphous powder (120mg). δH (DMSO-d^6, 390K), 7.71 (1H, br d, J 8.0Hz), 7.28 (2H, app.d J 7.0Hz), 7.22 (2H, app.t, J 7.0Hz), 7.15 (2H, d, J 8.3Hz), 6.94 (2H, d, J 8.3Hz), 5.18 (2H, s), 4.79-4.75 (1H, m), 4.77 (1H, d, J 9.2Hz), 4.45 (1H, sym.m), 4.33 (1H, d, J 9.2Hz), 3.21 (1H, dd, J 11.4, 7.3Hz), 3.09 (1H, dd, J 14.1, 5.1Hz), 2.95-2.86 (2H, m) 1.97(3H, s) and 1.75 (3H, s); m/z (ESI, 30V) 538 (MH+).

EXAMPLE 13

***N*-Acetyl-*D*-thioproline -(*N'*-2,4,6-trichlorobenzyl)-*L*-4-aminophenylalanine.**

Intermediate 5 was reacted with 2,4,6-trichlorobenzyl bromide in a similar manner to that described for Intermediate 21. Subsequent hydrolysis and purification as described for the compound of Example 5, followed by freeze drying afforded the title compound as a white amorphous solid (265mg). δH (DMSO-d^6, 1:1 ratio of rotamers) 8.33 (0.5H, d, J 8.0Hz), 8.04 (0.5H, d, J 8.0Hz), 7.69 (2H, s), 6.93 (2H, app.t, J 8.0Hz), 6.57 (2H, app.d, J 8.0Hz), 5.62 (1H, br s), 4.82-4.68 (2H, m), 4.45 (0.5H, d, J 8.7Hz), 4.43-4.30 (1H, m), 4.31 (2H, s), 4.22 (0.5H, d, J 9.6Hz), 3.29 (0.5H, dd, J

11.7, 7.3Hz), 3.12 (0.5H, dd, J 11.4, 7.3Hz), 3.00-2.69 (3H, m), 2.05 (1.5H, s) and 1.84 (1.5H, s); m/z (ES!, 60V) 530 (MH^+).

EXAMPLE 14

N-Acetyl-D-thioproline-(N'-2,6-dichlorobenzenesulphonyl)-L-4-aminophenylalanine

Intermediate 5 was reacted with 2,6-dichlorobenzenesulphonyl chloride in a similar manner to that described for Intermediate 2. The crude product was chromatographed (silica; EtOAc) to purity then hydrolysed with aqueous LiOH (as described for the compound of Example 5). Chromatography [silica; DCM (200), (MeOH (20), AcOH (3), H_2O (2)] and freeze-drying afforded the title compound as a white amorphous solid (270mg). δH (DMSO-d^6, 400K) 7.62 (1H, br d, J 8.0Hz), 7.54 (2H, app.d, J 7.7Hz), 7.47 (1H, app.t, J 7.7Hz), 7.08 (2H, d, J (8.9Hz), 7.03 (2H, d, J 8.9Hz), 4.80-4.73 (1H, m), 4.74 (1H, d, J 9.2Hz), 4.47 (1H, m), 4.33 (1H, d, J 9.2Hz), 3.18 (1H, dd, J 11.5, 7.4Hz), 3.05 (1H, dd, J 14.2, 5.3Hz), 2.96-2.84 (2H, m) and 1.95 (3H, s); m/z (ESI, 60V) 546 (MH^+).

EXAMPLE 15

N-Acetyl-D-thioproline-4-(2-methoxyphenylureido)-L-phenylalanine

A solution of Intermediate 5 (500mg, 1.42mmol) and 2-methoxyphenyl isocyanate (233mg, 208μl, 1.56mmol) in dry DCM (10ml) was stirred under N_2 at room temperature for 2h. The volatiles were removed *in vacuo* and the residue suspended in Et_2O. The obtained solid was filtered off with 10% aqueous HCl and Et_2O washing and sucked dry. This intermediate (560mg, 1.12mmol) was treated with $LiOH.H_2O$ (56mg, 1.33mmol) in dioxan (5ml), methanol (3ml) and water (5ml) at room temperature for 2h. A few drops of AcOH were added and the volatiles removed *in vacuo*. The residue was treated with Et_2O and water and filtered off with water washing to afford the title comound as an off-white powder (325mg). δH (DMSO-d^6, a 1:1 ratio of rotameric species) 9.28 (1H, s), 8.31 and 8.02 (1H, d, J 7.8Hz), 8.21 (1H, s), 8.11 (1H, d, J 7.6Hz), 7.40-7.28 (2H, m), 7.18-7.03 (2H, m), 7.02-6.86 (3H, m), 4.86-4.70 (2H, m), 4.46 (0.5H, d, J 8.8Hz), 4.43-4.31 (1H, m), 4.22 (0.5H, d, J 9.4Hz), 3.86 (3H, s), 3.37-2.78 (4H, m), 2.05 and 1.84 (3H, s); m/z (ESI, 60V) 487 (MH^+).

EXAMPLE 16

a) *N*-(Pyrid-4-oyl)-*D*-thioproline-(*O*-benzyl)-*L*-tyrosine

Intermediate 18 was coupled to isonicotinic acid in a similar manner to that described for Intermediate 19, and subsequently hydrolysed with aqueous LiOH in a similar manner to that described for the compound of Example 2a) to afford the title compound as a white solid (175mg). δH (DMSO-d^6, 400K), 8.65 (2H, d, *J* 6.1Hz), 7.78 (1H, d, *J* 8.0Hz), 7.45-7.25 (5H, m), 5.35 (2H, d, *J* 6.1Hz), 7.13 (2H, d, *J* 8.6Hz), 6.90 (2H, d, *J* 8.6Hz), 5.06 (2H, s), 4.86-4.73 (1H, m), 4.73 (1H, d, *J* 9.5Hz), 4.56-4.48 (1H, m), 4.46 (1H, d, *J* 9.4Hz), 3.29 (1H, dd, *J* 11.8, 7.4Hz) and 3.12-2.86 (3H, ms); m/z (ESI, 60V) 492 (MH^+).

The following compounds of Examples 16 b) - g) were prepared in a similar manner from Intermediate 18 and the appropriate acid:

b) *N*-(Pyrid-2-acetyl)-*D*-thioproline-(*O*-benzyl)-*L*-tyrosine

δH (DMSO-d^6) 8.45 (2H, d, *J* 4.8Hz), 7.72-7.67 (2H,m), 7.42-7.19 (7H, m), 7.12 (2H, d, *J* 8.5Hz), 6.88 (2H, d, *J* 8.5Hz), 5.05 (2H, s, CH_2O), 5.02-4.96 (1H, m, CHα-thiopro), 4.87 (1H, d, *J* 9.0Hz, $NC\underline{H}_AH_BS$), 4.57-4.51 (1H, m, CHα-tyr), 4.39 (1H, d, *J* 9.0Hz, $NCH_A\underline{H}_BS$), 3.85 (2H, M, CH_2pyr, 3.26-3.20 (1H, m, $CHC\underline{H}_AH_BS$), 3.09-3.03 (2H, m, $CHCH_A\underline{H}_BS$ + $C\underline{H}_AH_BAr$) amd 2.94-2.86 (1H, m, $CH_A\underline{H}_BAr$). m/z (ESI, 27V) 506 (MH^+).

c) *N*-(Pyrid-4-acetyl)-*D*-thioproline-(*O*-benzyl)-*L*-tyrosine

δH (DMSO-d^6) 8.46 (2H, dd), 7.77 (1H, br s), 7.43-7.29 (5H,m), 7.20 (2H, d), 7.13 (2H, d), 6.90 (2H, d), 5.05 (2H, s, CH_2O), 4.92-4.88 (1H,m), 4.42 (1H,d), 3.78-3.68 (2H, m), 3.28-3.22 (1H, m) and 3.09-2.87 (4H, m). m/z (ESI, 60V), 506 (MH^+).

d) *N*-(Indolyl-3-acetyl)-*D*-thioproline-(*O*-benzyl)-*L*-tyrosine

δH (DMSO-d^6, 400K) 10.51 (1H, br s, NH), 7.72 (1H, br d), 7.54 (1H, d, *J* 7.9Hz), 7.36 (6H, m), 7.18 (1H, d, *J* 2.3Hz), 7.11 (2H, d, *J* 8.6Hz), 7.07 (1H, m), 6.97 (1H,m), 6.89 (2H, d, *J* 8.6Hz), 5.05 (2H, s, CH_2O), 4.95 (1H, dd, *J* 7.4, 4.0Hz, CHα-thiopro), 4.87 (1H, d, *J* 9.2Hz, $NC\underline{H}_AH_BS$), 4.51 (1H, m, CHα-tyr), 4.43 (1H, d, *J* 9.2Hz,$NCH_A\underline{H}_BS$), 3.24 (2H, d, *J* 8.2Hz,

$CHC\underline{H}_2Ar$), 3.19 (2H, dd, $\underline{J}$ 11.5, 7.4Hz, $CHC\underline{H}_2S$) and 2.99 (2H, m, CH_2CO). $\underline{m/z}$ (ESI, 60V) 544 (MH^+).

e) *N*-(Benzothiophenyl-3-acetyl)-*D*-thioproline-(*O*-benzyl)-*L*-tyrosine

δH (DMSO-d^6, 390K) 7.92 (1H, m), 7.80 (2H, m),7.48 (1H, s), 7.37 (6H, m), 7.13 (2H, d, $\underline{J}$ 8.6Hz, Ar-H), 6.89 (2H, d, $\underline{J}$ 8.6Hz, Ar-H), 5.04 (2H, s, CH_2O), 4.97 (1H, dd, $\underline{J}$ 7.4, 4.0Hz, CHα-thiopro), 4.88 (1H, d, $\underline{J}$ 9.2Hz, $NC\underline{H}_AH_BS$), 4.52 (1H, m, CHα-tyr), 4.48 (1H, d, $\underline{J}$ 9.2Hz, $NCH_A\underline{H}_BS$), 3.94 (2H, m, $CHC\underline{H}_2Ar$), 3.27 (1H, dd, $\underline{J}$ 11.5, 7.4Hz, $C\underline{H}_AH_BS$) and 3.03 (3H, m, $CH_A\underline{H}_BS$ and CH_2CO). $\underline{m/z}$ (ESI, 60V) 561 (MH^+).

f) *N*-(Pyrid-3-propionyl)-*D*-thioproline-(*O*-benzyl)-*L*-tyrosine

δH (DMSO-d^6) 8.46 (1H, d, 8.37 (1H, d, $\underline{J}$ 3.4Hz), 7.60 (1H, d, $\underline{J}$ 7.8Hz), 7.71 (1H, d, NH), 7.42-7.21 (6H,m), 7.12 (2H, d, $\underline{J}$ 8.6Hz), 6.89 (2H, d, $\underline{J}$ 8.6Hz), 5.06 (2H, s, CH_2O), 4.88-4.74 (1H, m, CHα-thiopro), 4,79 (1H, d, $\underline{J}$ 9.2Hz, $NC\underline{H}_AH_BS$), 4.52 (1H, m, CHα-Tyr), 4.38 (1H, d, $\underline{J}$ 9.2Hz, $NCH_A\underline{H}_BS$), 3.24-3.17 (1H, m), 3.10-2.85 (5H, m) and 2.68 (2H, m). $\underline{m/z}$ (ESI, 60V) 520 (MH^+).

g) *N*-(Thiophen-3-acetyl)-*D*-thioproline-(*O*-benzyl)-*L*-tyrosine

δH (DMSO-d^6) 7.74 (1H, d), 7.44-7.22 (6H, m), 7.21 (1H, d, $\underline{J}$ 1.1Hz), 7.15-7.10 (2H, m), 7.01-6.99 (1H, m), 6.92-6.88 (2H, m), 5.06 92H, s, CH_2O), 4.91 (1H, m, CHα-Thiopro), 4.88 (1H, d, $\underline{J}$ 9.2Hz, $NC\underline{H}_AH_BS$), 4.55-4.47 (1H, m, CHα-tyr), 4.39 (1H, d, $\underline{J}$ 9.2Hz, $NCH_A\underline{H}_BS$), 3.75-3.60 (2H, m), 3.25-3.19 (1H, m) and 3.11-2.87 (3H, m). $\underline{m/z}$ (ESI, 60V) 511 (MH^+).

EXAMPLE 17

N-(4-Imidazoleacetyl)-*D*-thioproline-(*O*-2,6-dichlorobenzyl)-*L*-tyrosine

D-Thioproline-(*O*-2,6-dichlorobenzyl)-*L*-tyrosine methyl ester (prepared in a similar manner to Intermediate 18) was coupled to 1-trityl-4-imidazoleacetic acid in a similar manner to that described for Intermediate 19. Subsequent trityl removal (triethylsilane, TFA, DCM) and hydrolysis (aqueous LiOH; as described for the compound of Example 7) afforded the title compound as a white powder (235mg). δH (DMSO-d^6, 390K) 8.1 (1H, very br s), 7.96 (1H, br d, $\underline{J}$ 8.0Hz), 7.52-7.48 (3H, m), 7.46-7.40 (2H, m), 7.15 (2H, d, $\underline{J}$ 8.4Hz), 6.94 (2H, d, $\underline{J}$ 8.4Hz), 6.89 (2H,s), 5.25 (2H, s),

5.01 (1H, dd, J 7.3, 3.7Hz), 4.86 (1H, d, J 9.0Hz), 4.58-4.47 (1H, m), 4.38 (1H, d, J 9.0Hz), 3.69 (1H, d, J 15.7Hz), 3.56 (1H, d, J 15.7Hz), 3.20 (1H, dd, J 11.4, 7.3Hz), 3.11-2.99 (2H, m) and 2.91 (1H, dd, J 14.0, 8.4Hz); m/z (ESI, 60V) 561 (MH^+).

EXAMPLE 18

N-(Pyrid-3-oyl)-D-thioproline-(O-benzyl)-L-tyrosine

Intermediate 18 was coupled to nicotinic acid in a similar manner to that described for Intermediate 19, and subsequently hydrolysed with aqueous LiOH, as described for the compound of Example 7, to afford the title compound. δH (DMSO-d^6) 8.78-8.55 (2H, br m), 8.38 (1H, br d J 7.8Hz), 8.21-7.25 (7H, m), 7.11 (2H, d, J 8.5Hz), 6.85 (2H, br d, J 8.0Hz), 5.02 (2H, s), 5.03-4.3 (4H, m), 3.40-3.22 (1H, br m), 3.03 (1H, dd, J 13.8, 4.6Hz) and 2.90-2.75 (2H, m); m/z (ESI), 492 (MH^+).

EXAMPLE 19

N-Acetyl-D-thioproline-L-4-benzoylphenylalanine

Intermediate 20 (503mg, 1.14mmol) was treated with a solution of LiOH. H_2O(1.38mmol) in 50% aqueous dioxane (20ml) at room temperature for 2h. The pH was adjusted to 3 with concentrated HCl and the volatiles removed *in vacuo*. The residue was chromatographed [silica; DCM (200), MeOH (20), AcOH (3), H_2O (2)] to afford the product as a colourless oil. Freeze-drying from aqueous methanol afforded the title compound as a white amorphous solid: δH (DMSO-d^6 approximately 1.6:1 ratio of rotameric species) 7.79-7.69(4H, m), 7.68-7.61 (1H, m), 7.58-7.48 (2H, m), 7.45-7.36 (2H, m), 4.85-4.68 (3H, m), 4.57-4.42 (1H, d, J 9.0Hz), 3.48-3.08 (3H, ms), 2.98 and 2.89 (1H, dd, J 11.9, 4.0Hz, 2.14 and 1.92 (3H, s); m/z (ESI, 27V) 427 (MH^+).

EXAMPLE 20

N-(N-Acetyl-D--5,5-dimethyl-1,3-thiazolidin-4-oyl)-(O-benzyl)-L-tyrosine

Intermediate 22 (340mg, 0.72mmol) was treated with a solution of LiOH. H_2O (36mg, 0.86mmol) in MeOH (2ml), dioxane (2ml) and H_2O (3ml) at room temperature for 1.5h. A few drops of acetic acid were added and the volatiles were removed *in vacuo*. The crude product was

chromatographed [silica; DCM (200), MeOH (20), AcOH (3), H_2O (2)] to afford the product as a colourless oil. Freeze-drying from aqueous methanol afforded the title compound as a white amorphous solid (240mg, 73%). δH (DMSO-d^6, approximate 1.3:1 ratio of rotamers) 8.29 (1H major, d, *J* 8.4Hz), 8.06 (1H minor, d, *J* 8.0Hz), 7.44-7.28 (5H, m), 7.20-7.10 (2H, m), 6.93-6.85 (2H, m), 5.07 (2H major, s), 5.06 (2H minor, s), 4.73 (1H minor, d, *J* 8.7Hz), 4.70 (1H minor, d, *J* 8.7Hz), 4.63 (1H major d, *J* 9.8Hz), 4.55 (1H major, d, *J* 9.8Hz), 4.50-4.24 (2H, m's), 3.09 (1H major, dd, *J* 13.9, 4.1Hz), 2.96 (1H minor, dd, *J* 13.9, 5.1Hz), 2.85-2.75 (1H, m), 2.03 (3H minor, s), 1.81 (3H major, s) and 1.35, 1.00 and 0.91 (6H, singlets); m/z (ESI, 60V) 457 (MH^+).

EXAMPLE 21

***N*-Acetyl-*D,L*-homothioproline-(*O*-2,6-dichlorobenzyl)-*L*-tyrosine**

N-Acetyl-*D,L*-homothioproline (prepared *via* (1) bromopyruvate, 2-aminoethanethiol hydrochloride, EtOH; (2) $NaBH_4$, EtOH; (3) acetic anhydride, DCM; (4) LiOH, aqueous EtOH) was coupled to *O*-(2,6-dichlorobenzyl)-*L*-tyrosine methyl ester hydrochloride in a similar manner to that described for Intermediate 19, affording the methyl ester of the title compound. Subsequent hydrolysis with aqueous LiOH and purification, similar to that described for the compound of Example 5, afforded the title compound as a white amorphous solid (850mg). δH (DMSO-d^6, 390K, mixture of diastereoisomers) 7.49 (2H, approximate d, *J* 8.7Hz), 7.45 (1H, br s), 7.43 (1H, approximate t, *J* 8.7Hz), 7.19 and 7.17 (2H, d, *J* 8.7Hz), 6.95 and 6.94 (2H, d, *J* 8.7Hz), 5.25 (2H, s), 5.02 (1H, br m), 4.60-4.52 (1H, m), 4.23-4.02 (1H, br m), 3.45-2.92 (4H, m), 2.81 and 2.77 (1H, d, *J* 4.7Hz) and 2.70-2.41 (2H, m); m/z (ESI, 60V) 511 (MH^+).

EXAMPLE 22

***N*-(4-Morpholinoacetyl)-*D*-thioproline-(*O*-2,6-dichlorobenzyl)-*L*-tyrosine hydrochloride**

Intermediate 23 (618mg, 1.04mmol) was treated with $LiOH.H_2O$ (96mg, 2.29mmol) in dioxane (10ml), MeOH (5ml) and water (5ml) for 1.5h at room temperature. A few drops of acetic acid were added and the volatiles removed *in vacuo*. The residue was chromatographed [silica; DCM (300 to 200), MeOH (20), AcOH (3), H_2O (2)] to afford the pure

product as an oil. This was dissolved in aqueous dioxane, acidified with a few drops of concentrated HCl and evaporated *in vacuo*. The HCl salt was re-dissolved in water and freeze-dried to afford the title compound as a white amorphous solid (302mg, 47%). δH (DMSO-d^6, 390K) 8.21 (1H, br s), 7.50 (2H, approximate t, J 8.0Hz), 7.41 (1H, approximate t. J 8.0Hz), 7.19 (2H, d, J 8.6Hz), 6.96 (2H, d, J 8.6Hz), 5.25 (2H, s), 4.98 (1H, dd, J 7.3, 4.3Hz), 4.79 (1H, d, J 9.2Hz), 4.58-4.49 (1H, m), 4.47 (1H, d, J 9.2Hz), 4.23-4.18 (1H, m), 4.05-3.90 (1H, m), 3.88 (4H, t, J 4.7Hz), 3.30 (1H, dd, J 11.6, 7.4Hz), 3.31-3.14 (4H, br m), 3.11 (1H, dd, J 14.2, 5.3Hz), 3.00-2.92 (2H, m); m/z (ES+, 60V) 582 (MH^+).

EXAMPLE 23

N-Acetyl-D-thioproline-(N'-2,6-dichlorobenzoyl-N'methyl)-L-4-aminophenylalanine

Intermediate 25 was reacted with 2,6-dichlorobenzoyl chloride in a similar manner to that described for Intermediate 2. Purification by flash chromatography (silica; 3:97 MeOH/DCM) and subsequent hydrolysis with aqueous LiOH (as described for the compound of Example 5) afforded the title compound as a white foam (750mg). δH (DMSO-d^6, (two pairs of rotameric species.) 8.50, 8.40, 8.22 and 8.16 (1H, d, J 8.0Hz), 7.62-7.08 (7H, m), 4.82-4.30 (3H, m), 4.45, 4.39, 4.21 and 4.17 (1H, d, J 8.4Hz), 3.34 and 3.10 (3H, s), 3.30-2.50 (4H, m), 2.05, 2.03, 1.83 and 1.79 (3H, s); m/z (ES1, 30V) 524 (MH^+).

EXAMPLE 24

N-Acetyl-D-thioproline-(N'-2,6-dichlorobenzyl-N'-methyl)-L-4-aminophenylalanine

Intermediate 25 was reacted with 2,6-dichlorobenzyl bromide and purified in a similar manner to that described for Intermediate 21. Subsequent hydrolysis with aqueous LiOH (as described for the compound of Example 2a) afforded the title compound as an off-white solid (450mg). δH (DMSO-d^6, 1:1 ratio of rotamers) 8.38 and 8.10 (1H,d, J 8.3Hz), 7.51 (2H, d, J 7.9Hz), 7.38 (1H, t, J 7.9Hz), 7.05 (2H, app.t J 8.2Hz), 6.84 (2H, app. d, J 8.2Hz), 4.82-4.68 (2H, ms), 4.55 (2H, s), 4.44 (0.5H, d, J 9.2Hz), 4.45-4.32 (1H, m), 4.22 (0.5H, d, J 9.8Hz), 3.40-2.67 (4H, m), 2.60 (3H, s), 2.04 and 1.83 (3H, s); m/z (ESI, 60V) 510 (MH^+).

EXAMPLE 25

***N*-Acetyl-*D*-thioproline-4-(carbobenzyloxy)phenylalanine**

The title compound was prepared as a white solid by acylation of Intermediate 27 with *N*-acetyl-*D*-thioproline in a similar manner to the preparation of Intermediate 1 followed by hydrolysis of the resulting ester in a similar manner to the compound of Example 2a) using potassium carbonate in place of lithium hydroxide. δH (DMSO-d^6, 390K) 7.9 (2H, dt, J 6.5, 1.8Hz), 7.46-7.31 (7H, m), 5.36 (2H, s), 4.80 (1H, m), 4.75 (d, J 9.1Hz) and 4.73 (d, J 9.2Hz) together (1H), 4.59 (1H, m), 4.41 (d, J, Hz) and 4.34 (d, J 9.2Hz), together (1H), 3.30-3.19 (2H, m), 3.11-2.95 (2H, m), 1.98 (s) and 1.97 (s) together (3H); m/z (ESI. 60V) 457 (MH^+).

EXAMPLE 26

***N*-Acetyl-*D*-thioproline-(*N*'-benzenesulphonyl)-*L*-4-aminophenylalanine**

A solution of Intermediate 61 (0.63g, 1.37mmol), in THF (20ml) and water (10ml) was treated with LiOH. H_2O (69mg, 1.65mmol) and stirred at room temperature for 16h. The reaction was acidified to pH1 with 10% HCl and extracted twice with DCM. The combined organic extracts were dried ($MgSO_4$) and evaporated *in vacuo* to give a foam that was purified by chromatography (SiO_2; DCM/MeOH/AcOH 90:10:1). The product was lyophilised from CH_3CN/ water (3:2, 20ml) to give the title compound as a fluffy white solid (0.25g, 41%). δH (DMSO-d^6, 390K) 7.77-7.73 (2H, m, Ar-H), 7.61 (1H, br s, NH), 7.58-7.47 (3H, m, Ar-H), 7.07 (2H, d, J 8.7Hz, Ar-H), 7.01 (2H, d, J 8.7Hz, Ar-H), 4.74 (1H, m, CHα-Thiopro), 4.76 (1H, d, J 9.2Hz, NC$\underline{H}_A$$H_B$S), 4.42 (1H, dt, J 8.3, 5.3Hz, CHα-Ph), 4.32 (1H, d, J 9.2Hz, NC$H_A$$\underline{H}_B$S), 3.20 (1H, dd, J 11.5, 7.4Hz, CHC$\underline{H}_A$$H_B$S), 3.04 (1H, dd, J 14.1, 5.3Hz, ArC$\underline{H}_A$$H_B$),2.94 (1H, dd, J 11.5, 3.9Hz, CHC$H_A$$\underline{H}_B$S), 2.88 (1H, dd, J 14.1, 8.5Hz, ArC$H_A$$\underline{H}_B$) and 1.95 (3H, s, COMe). m/z (ESI, 30V) 478 (MH^+).

The following compounds of Examples 27-52 were prepared by acylation of an appropriate amine starting material (deprotected as necessary) using the acid indicated in a similar manner to the preparation of Intermediate 1

followed by hydrolysis of the resulting ester in a similar manner to the preparation of the compound of Example 2a):

EXAMPLE 27

***N*-(*N*-Acetyl-2-phenyl-*D*-1,3-thiazolidin-4-oyl)-(*O*-benzyl-*L*-tyrosine**

from Intermediate 53 and *O*-benzyl-*L*-tyrosine methyl hydrochloride ester δH (DMSO-d^6) 7.82 (1H, br d, J 7.6Hz, NH), 7.61 (2H, m, Ar-H), 7.31 (8H, m, Ar-H), 7.14 (2H, d, J 8.7Hz, Ar-H), 6.89 (2H, d, J 8.7Hz, Ar-H), 6.28 (1H, s, NCH(Ph)S), 5.04 (2H, s, CH_2O), 4.87 (1H, t, J 6.9Hz, CHα-thiopro), 4.59 (1H, m, CHα-tyr), 3.24 (1H, dd, J 11.8, 6.8Hz, $CHCH_AH_BS$), 3.05 (2H, m, $CHCH_AH_BS$ and $CHCH_AH_BAr$), 2.93 (1H, dd, J 14.1, 8.3Hz, $CHCH_AH_BAr$) and 1.89 (3H, s, COMe). m/z (ESI, 160V) 505 (MH^+).

EXAMPLE 28

***N*-(*N*-Acetyl-5-phenyl-1,3-thiazolidin-4-oyl-(*O*-2,6-dichlorobenzyl)-*L*-tyrosine**

Prepared as 2-diastereomeric species, from Intermediate 55 and (*O*-2,6-dichlorobenzyl)-*L*-tyrosine methyl ester hydrochloride.

Diastereomer 1

δH (DMSO-d^6, 390K) 7.73 (1H, br s, NH), 7.51-7,40 (3H, m, Ar-H), 7.38-7.23 (5H, m, Ar-H), 7.18 (2H, d, J 8.7Hz, Ar-H), 6.96 (2H, d, J 8.7Hz, Ar-H), 5.26 (2H, s, CH_2O), 4.97 (1H, d, J 9.2Hz, NCH_AH_BS), 4.86 (1H, m, CHα-thiopro), 4.76 (1H, d, J 3.5Hz, CH-Ph), 4.54 (1H, m, CHα-tyr), 4.53 (1H, d, J 9.2Hz, NCH_AH_BS), 3.11 (1H, dd, J 14.1, 5.3Hz, CH_AH_BAr), 2.96 (1H, dd, J 14.1, 8.6Hz, CH_AH_BAr), 2.00 (3H, br s, COMe). m/z (ESI, 60V) 573 (MH^+)

Diastereomer 2

δH (DMSO-d^6, 390K) 7.83 (1H, br s, NH), 7.51-7.40 (3H, m, Ar-H), 7.34-7.27 (5H, m, Ar-H), 7.14 (2H, d, J 8.7Hz, Ar-H), 6.94 (2H, d, J 8.7, Ar-H), 5.25 (2H, s, CH_2O), 4.98 (1H, d, J 9.0Hz, NCH_AH_BS), 4.88 (1H, m, CHα-thiopro), 4.68 (1H, d, J 3.6Hz, CH-Ph), 4.55 (2H, m, CHα-tyr and NCH_AH_BS), 3.08 (1H, dd, J 14.2, 5.3Hz, CH_AH_BAr), 2.93 (1H, dd, J 14.2, 8.5Hz, CH_AH_BAr) and 2.01 (3H, br s, COMe). m/z (ESI, 60V) 573 (MH^+).

EXAMPLE 29

N-Acetyl-(1-thia-3-azaspiro[4.4]non-4-oyl)-(O-2,6-dichlorobenzyl)-L-tyrosine

Prepared as 2 diastereomers [separated by fractional recrystalisation (ispropanol/water)] from Intermediate 57 and (*O*-2,6-dichlorobenzyl)-*L*-tyrosine methyl ester hydrochloride.

Diastereomer 1

δH (DMSO-d^6, 390K) 7.56 (1H, br s, NH), 7.52-7.39 (3H,m, Ar-H), 7.20 (2H, d, *J* 8.7Hz, Ar-H), 6.95 (2H, d, *J* 8.7Hz, Ar-H), 5.25 (2H, s, CH_2O), 4.64 (2H, s, NCH_2S), 4.61 (1H, m, CHα-thiopro), 4.43 (1H, m, CHa-tyr), 3.11 (1H, dd, *J* 14.2, 5.2Hz, CHC$\underline{H}_A$H$_B$Ar), 2.94 (1H, dd, *J* 14.2, 8.6Hz, CHCH$_A\underline{H}_B$Ar) and 1.92-1.45 (11H, m, CH_2,COMe). m/z (ESI, 60V) 551 (MH^+).

Diastereomer 2

δH (DMSO-d^6, 400K) 7.51 (1H, br s, NH), 7.48-7.39 (3H, m, Ar-H), 7.17 (2H, d, *J* 8.7, Ar-H), 6.95 (2H, d, *J* 8.7Hz, Ar-H), 5.26 (2H, s, CH_2O), 4.69-4.45 (4H, m, CHα-thiopro, CHα-tyr, NC$\underline{H}_2$S), 3.10 (1H, dd, *J* 14.2, 5.2Hz, C$\underline{H}_A$H$_B$Ar), 2.92 (1H, dd, *J* 14.2, 8.7Hz, CH$_A\underline{H}_B$Ar), 1.96 (3H, s, COMe), 1.95-1.54 (8H, m, CH_2). m/z (ESI, 60V) 551 (MH^+).

EXAMPLE 30

N-(N-Acetyl-L-5,5-dimethyl-1,3-thiazolidin-4-oyl)-O-benzyl-L-tyrosine

from Intermediate 42a) and *O*-benzyl-*L*-tyrosine methyl ester hydrochloride as a white solid. δH (DMSO-d^6, 400K) 7.58 (1H, br d, CONH), 7.44-7.30 (5H, m, Ph), 7.17 (2H, d, *J* 8.7Hz, ArH), 6.91 (2H, d, *J* 8.7Hz, ArH), 5.08 (2H, s, OC$\underline{H}_2$Ph), 4.73 (1H, d, *J* 9.2Hz, NC$\underline{H}_A$H$_B$S), 4.65 (1H, d, *J* 9.1Hz, NCH$_A\underline{H}_B$S), 4.93 (1H, dt, *J* 8.2, 5.5 CHα-tyr), 4.36 (1H, s, CHα), 3.08 (1H, dd, *J* 14.2, 5.4Hz, CHC$\underline{H}_A$H$_B$), 2.93 (1H, dd, *J* 14.2, 8.2Hz, CHCH$_A\underline{H}_B$), 1.90 (3H, br s, $COCH_3$), 1.50 (3H, s, C$\underline{Me}_A$Me$_B$) and 1.28 (3H, s, CMe$_A\underline{Me}_B$); m/z (ESI, 160V) 457 (MH^+).

EXAMPLE 31

N-(N-Acetyl-D-5,5-dimethyl-1,3-thiazolidin-4-oyl)-O-(2,6-dichlorobenzyl)-L-tyrosine

from Intermediate 42b) and (*O*-2,6-dichlorobenzyl)-*L*-tyrosine methyl ester. δH (DMSO-d^6, 390K) 7.68 (1H, br s, CONH), 7.51-7.48 (2H, m, Cl_2ArH),

7.41 (1H, dd, J 9.3, 6.5Hz, Cl_2ArH), 7.18 (2H, d, J 8.6Hz, ArH), 6.95 (2H, d, J 8.6Hz, ArH), 5,26 (2H, s, $O C\underline{H}_2 Ar$), 4.74 (1H, d, J 9.2Hz, $NC\underline{H}_{AB}S$), 4.64 (1H, d, J 9.3Hz, $NCH_A\underline{H}_BS$), 4.6 (1H, br m, CHαtyr), 4.35 (1H, s, CHα), 3.11 (1H, dd, J 14.2, 5.3Hz, $CHC\underline{H}_AH_B$), 2.92 (1H, dd, J 14.2, 8.7Hz, $CHCH_A\underline{H}_B$), 1.95 (3H, s, $COCH_3$), 1.45 (3H, s, $C\underline{Me}_AMe_B$) and 1.19 (3H, s, $CMe_A\underline{Me}_B$); m/z (ESI, 60V) 525 (MH^+).

EXAMPLE 32

N-Acetyl-D-thioproline-4[2-(1-phenylethyl)]-L-phenylalanine

from Intermediate 41 and N-acetyl-D-thioproline. δH (DMSO-d^6, 400K) 7.66 (1H, br d, CONH), 7.28-7.11 (9H, m, ArH), 4.82 (1H, dd, J 7.5, 3.8Hz, CHαthiopro), 4.76 (1H, d, J 9.2Hz, $NC\underline{H}_AH_BS$), 4.53 (1H, dt, J 8.3, 5.4Hz, CHαPh), 4.36 (1H, d, J 9.2Hz, $NCH_A\underline{H}_BS$), 3.23 (1H, d, $CHC\underline{H}_AH_BS$), 3.11 (1H, d, J 14.1, 5.4Hz, $CHC\underline{H}_AH_BAr$), 3.00-2.93 (2H, m, $CHCH_A\underline{H}_BS$ + $CHCH_A\underline{H}_BAr$), 2.90 (4H, s, $C\underline{H}_2C\underline{H}_2$) and 1.98 (3H, s $COCH_3$); m/z (ESI, 15V) 427 (MH^+).

EXAMPLE 33

N-Acetyl-D-thioproline-4-phenyl-L-phenylalanine

from Intermediate 33 and N-acetyl-D-thioproline. δH (DMSO-d^6, 400K) 7.75 (1H, br d, CONH), 7.62-7.29 (9H, m, ArH), 4.83 (1H, dd, J 7.2, 3.9Hz. CHαthiopro), 7.76 (1H, d, J 9.2Hz, $NC\underline{H}_AH_BS$), 4.59 (1H, dt, J 8.4, 5.4Hz, CHαPh), 4.37 (1H, d, J 9.2Hz, $NCH_A\underline{H}_BS$), 3.28-3.16 (2H, m, $CHC\underline{H}_AH_BS$ + $C\underline{H}_AH_BAr$), 3.06-2.98 (2H, m, $CHCH_A\underline{H}_BS$ + $CH_A\underline{H}_BAr$) and 1.98 (3H, s, $COCH_3$); m/z (ESI, 15V) 399 (MH^+).

EXAMPLE 34

N-Acetyl-D-thioproline-4-(3-prop-1-enyl)-L-phenylalanine

from Intermediate 34 and N-acetyl-D-thioproline. δH (DMSO-d^6, 400K) 7.69 (1H, br d, CONH), 7.14 (2H, d, J 8.2Hz, ArH), 7.09 (2H, d, J 8.3Hz, ArH), 6.04-5.90 (1H,tdd, J 17.0, 10.2, 6.7Hz, $CH_2C\underline{H}=CH_2$), 5.10-5.03 (2H, m, $CH_2CH=C\underline{H}_2$), 4.81 (1H, dd, J 7.5, 3.9Hz, CHαthiopro), 4.76 (1H, d, J 9.2Hz, $NC\underline{H}_AH_BS$), 4.53 (1H, dt, J 8.3, 5.4Hz, CHαPh), 4.36 (1H, d, J 9.5Hz, $NCH_A\underline{H}_BS$), 3.34 (2H, d, J 6.6Hz, $C\underline{H}_2CH=CH_2$), 3.23 (1H, dd, J 11.5, 7.4Hz, $CHC\underline{H}_AH_BS$), 3.11 (1H, dd, J 14.1, 5.5Hz, $CHCH_A\underline{H}_BAr$),

3.00-2.91 (2H, m, CHCH$_A\underline{H}_B$S + CHCH$_A\underline{H}_B$Ar) and 1.97 (3H, s, $COCH_3$); m/z (ESI, 15V) 363 (MH^+).

EXAMPLE 35

***N*-Acetyl-*D*-thioproline-4-(2-benzo[b]furanyl)-*L*-phenylalanine**

from Intermediae 35 and *N*-acetyl-*D*-thioproline. δH (DMSO-d^6, 400K) 7.80 (2H, d, J 8.4Hz, ArH), 7.75 (1H, v br d, CONH), 7.65-7.55 (2H, m ArH), 7.35 (2H, d, J 8.5Hz, ArH), 7.33-7.22 (3H, m, ArH + C=C$\underline{H}$), 4.84 (1H, dd, J 7.4, 3.9Hz, CHαthiopro), 4.76 (1H, d, J 9.2Hz, NC$\underline{H}_A$H$_B$S), 4.60 (1H, dt, J 8.3, 5.4Hz, CHαPh), 4.38 (1H, d, J 9.1Hz, NCH$_A\underline{H}_B$S), 3.29-3.18 (2H, m, 2 x CHC$\underline{H}_A$H$_B$), 3.09-3.01 (2H, m, 2 x CHCH$_A\underline{H}_B$) and 1.99 (3H, s, $COCH_3$); m/z (ESI, 15V) 439 (MH^+).

EXAMPLE 36

***N*-Acetyl-*D*-thioproline-4[2-(1-phenylethenyl)]phenylalanine**

from Intermediate 36 and *N*-acetyl-*D*-thioproline. δH (DMSO-d^6, 400K) (mixture of 2 diastereoisomers) 7.71 (1H, br, CONH), 7.57-7.21 (9H, m, ArH), 7.15 (2H, s,C$\underline{H}$=C$\underline{H}$), 4.82 (1H, dd, CHαthiopro), 4.77 and 4.75 (1H, each d, J 9.2Hz, NC$\underline{H}_A$H$_B$S), 4.58 (1H, m, CHαPh), 4.38 and 4.36 (1H, each d, J 9.2Hz. NCH$_A\underline{H}_B$S), 3.29-2.96 (4H, m, CHC$\underline{H}_2$Ar + CHC$\underline{H}_2$S), 1.99 and 1.96 (3H, each s, $COCH_3$); m/z (ESI, 15V) 425 (MH^+).

EXAMPLE 37

***N*-Acetyl-*D*-thioproline-4-(3-pyridyl)phenylalanine**

from Intermediate 37 and *N*-acetyl-*D*-thioproline. δH (DMSO-d^6, 400K) 8.82 (1H, d, J 1.8Hz, PyH), 8.53 (1H, dd, J 4.7, 1.5Hz, PyH), 7.96 (1H, ddd, J 8.0, 2.3, 1.8Hz, PyH), 7.53 (2H, d, J 8.2Hz, ArH), 7.5 (1H, br, CONH), 7.41 (1H, dd, J 7.9, 4.0Hz, PyH), 7.35 (2H, d, J 8.3Hz, ArH), 4.82 (1H, dd, CHαthiopro), 4.77 (1H, d, J 9.2Hz, NC$\underline{H}_A$H$_B$S), 4.37 (1H, d, J 9.3Hz, NCH$_A\underline{H}_B$S), 3.27-3.21 (2H, m, 2 x CHC$\underline{H}_A$H$_B$),3.10-3.04 (2H, m, 2 x CHCH$_A\underline{H}_B$) and 1.97 (3H, s, $COCH_3$); m/z (ESI, 27V) 400 (MH^+).

EXAMPLE 38

***N*-Acetyl-*D*-thioproline-*L*-phenylalanine**

from *N*-acetyl-*D*-thioproline and *L*-phenylalanine methyl ester hydrochloride. δH (DMSO-d^6, 400K) 7.69 (1H, br d, CONH), 7.29-7.17

(5H, m, ArH), 4.82 (1H, dd, J 7.4, 3.9Hz, CHαthiopro), 4.77 (1H, d, J 9.2Hz, NC$\underline{H}_A$$H_B$S), 4.56 (1H, dt, J 8.3, 5.4Hz, CHαPh), 4.37 (1H, d, J 9.3Hz, NC$H_A$$\underline{H}_B$S), 3.24 (1H, dd, J 11.5, 7.4Hz, CHC$\underline{H}_A$$H_B$S), 3.15 (1H, dd, J 14.1, 5.4Hz, CHC$\underline{H}_A$$H_B$Ar), 2.99 (1H, dd, J 11.6, 3.9Hz, CHC$H_A$$\underline{H}_B$S), 2.98 (1H, dd, J 14.1, 8.4Hz, CHC$H_A$$\underline{H}_B$Ar) and 1.98 (3H, $COCH_3$); m/z (ESI, 27V) 323 (MH^+).

EXAMPLE 39

***N*-Acetyl-*D*-thioproline-*N*-methyl-*N*'-(3,5-dichloro-isonicotinoyl)-*L*-4-aminophenylalanine**

from Intermediate 51 and *N*-acetyl-*D*-thioproline. δH (DMSO-d^6, 420K) 10.39 (1H, br s, CONH) 8.67 (2H, s, Pyr$\underline{H}$), 7.54 (2H, d, J 7.7Hz, ArH), 7.25 (2H, d, J 8.1Hz, ArH), 5.14 (1H, dd,CHα), 5.03 (1H, dd, CHα), 3.35-3.23 (2H, m, 2 x CHC$\underline{H}_A$$H_B$), 3.05 (1H, dd, J 14.6, 10.2Hz, CHC$H_A$$\underline{H}_B$), 2.93 (3H, s, NMe), 2.8-2.7 (1H, br m, CHC$H_A$$\underline{H}_B$) and 1.91 (3H, br s, $COCH_3$); m/z (ESI,70V) 525 (MH^+).

EXAMPLE 40

***N*-Acetyl-*D*-thioproline-4-(2-hydroxyhexafluoroisopropyl)-DL-phenyl alanine**

from Intermediate 67 and *N*-acetyl-*D*-thioproline δH (DMSO-d^6, 390K) 7.90-7.75 (1H, m, NH), 7.59 (2H, d, J 7.9Hz, ArH), 7.35 (2H, dd, J 8.5, 3.3Hz, ArH), 4.90-4.80 (1H, m, NC$\underline{H}_A$$H_B$S), 4.74 (1H, dd, J 9.2, 7.3Hz, NC$H_A$$\underline{H}_B$S), 4.67-4.55 (1H, m, α-CH), 4.33 (1H, dd, J 11.1 and 9.2Hz, α-CH), 3.29-2.89 (4H, m, C$\underline{H}_2$Ar and SC$\underline{H}_2$CH) and 1.96 (s) and 1.93 (s); together (3H, $COCH_3$); m/z (ESI, 60V) 489 (MH^+).

EXAMPLE 41

***N*-Acetyl-*D*-thioproline-4-(trifluoromethyl)-DL-phenylalanine**

from 4-(trifluoromethyl)-*DL*-phenylalanine methyl ester and *N*-acetyl-D-thioproline δH (DMSO-d^6) 8.56-8.12 (1H, m,NH), 7.68-7.55 (2H, m, ArH), 7.51-7.37 (2H, m, ArH),4.85-4.15 (4H, m, NC$\underline{H}_2$S and 2 x α-CH), 3.40-2.65 (4H, m,SC$\underline{H}_2$CH and C$\underline{H}_2$Ar),2.06 (s) and 2.04 (s) and 1.80(s) and 1.71 (s); together (3H, $COCH_3$); m/z (ESI, 60V), 391 (MH^+).

EXAMPLE 42

***N*-Acetyl-*D*-thioproline -4-(tert-butyl)-DL-phenylalanine**

from 4-(tert-butyl)-DL-phenlalanine methyl ester and *N*-acetyl-*D*-thioproline δH (DMSO-d^6) 8.45-8.03 (1H, m, NH), 7.33-7.07 (4H, m, ArH), 4.87-4.17 (4H, m, NC$\underline{H}_2$S and 2 x α-CH), 3.90-2.51 (4H, m, C$\underline{H}_2$Ar and SC$\underline{H}_2$CH), 2.07 (s) and 1.99 (s) and 1.79 (s) and 1.69 (s); together (3H, COC$\underline{H}_3$) and 1.25 (9H, s, ^{t}Bu). m/z (ESI, 60V) 379 (MH^+).

EXAMPLE 43

***N*-Acetyl-*D*-thioproline-4-{[(2,6-dichlorophenyl)sulphonyl]methyl} phenylalanine**

from Intermediate 71 and *N*-acetyl-*D*-thioproline δH (DMSO-d^6) 8.60-8.14 (1H, m, NH), 7.73-7.61 (2H, m, ArH), 7.54-7.37 (5H, m, ArH), 4.87 (2H,s, C$\underline{H}_2$$SO_2$), 4.80-4.16 (4H, m, 2 x α-CH and NC$\underline{H}_2$S), 3.40-2.72 (4H, m, SC$\underline{H}_2$CH and CH_2Ar), 2.12-1.80 (3H, m, $COCH_3$) m/z (ESI, 60V) 545 (MH^+).

EXAMPLE 44

***N*-Acetyl-*D*thioproline-4-[(2,6-dichlorobenzyl)-sulphonyl] phenylalanine**

from Intermediate 72 and *N*-acetyl-*D*-thioproline δH (DMSO-d^6) 8.46-8.05 (1H, m, NH), 7.65-7.61 (3H, m, ArH), 7.20-7.10 (4H, m, ArH), 4.82-4.61 (4H, m, SO_2C$\underline{H}_2$ and SC$\underline{H}_2$N), 4.44-4.37 (1H, m, α-CH), 4.23 (1H, dd, J 18.7, 9.8Hz, α-CH), 3.50-2.72 (4H, m, SC$\underline{H}_2$CH and C$\underline{H}_2$Ar) and 2.06 (s) and 2.05 (s) and 1.82 (s) and 1.77 (s) together (3H, $COCH_3$); m/z (ESI, 60V) 545 (MH^+).

EXAMPLE 45

***N*-Acetyl-*D*-thioproline-4-([3,5-dichlorophenyl]carboxamido)phenyl alanine**

from Intermediate 30 and *N*-acetyl-*D*-thioproline. δH (DMSO-d^6, 390K) 10.1 (1H, br s), 7.9-7.8 (4H,m), 7.76 (1H, v br s), 7.39 (2H, m), 7.21 (1H, t, J 1.9Hz), 4.82 (1H, br m), 4.77 (d, J 9.2Hz) and 4.75 (d, J 9.2Hz) together (1H), 4.62 (1H, br m), 4.37 (1H, d, J 9.2Hz), 3.28-3.20 (2H, br m), 3.12-2.98 (2H, br m) and 1.99 (s) and 1.67 (s) together (3H). m/z (ESI, 60V) 510 (MH^+).

EXAMPLE 46

***N*-Acetyl-*D*-thioproline (*N'*-acetyl)-*L*-4-amino phenylalanine**

from 4-(*N*-acetyl)-*L*--4-amino phenylalanine methylester and *N*-acetyl-*D*-thioproline δH (DMSO-d^6, 390K) 9.37 (1H, br s, NH), 7.8-7.62 (1H, m, NH), 7.44 (2H, d, *J* 8.5Hz, ArH), 7.10 (2H, d, *J* 8.5Hz, ArH), 4.88-4.71 (2H, m, NCH_2S), 4.58-4.45 (1H, m, α-CH), 4.36 (1H, d, *J* 9.2Hz, α-CH), 3.24 (1H, dd, *J* 11.5, 7.4Hz), 3.07 (1H, dd, *J* 14.1, 5.4Hz), 3.00 (1H, dd, *J* 11.5, 3.9Hz), 2.92 (1H, dd, *J* 14.1, 8.4Hz), and 2.02 (3H, s, $COC\underline{H}_3$) and 1.98 (3H, s, $COC\underline{H}_3$); *m/z* (ESI, 60V), 380 (MH^+),

EXAMPLE 47

***N*-Acetyl-*D*-thioproline-(*N'*-2,6-dimethoxybenzoyl)-*L*--4-amino phenylalanine**

from (*N*-2,6-dimethoxybenzoyl)-*L*-4-amino-phenylalanine methyl ester and *N*-acetyl-*D*-thioproline δH (DMSO-d^6) 10.10 (1H, s, NH), 8.44 (d, *J* 7.9Hz) and 8.12 (d, *J* 8.3Hz); together (1H,NH), 7.56-7.54 (2H, m, ArH), 7.33 (1H, t, *J* 8.4Hz, $Ar(OMe)_2\underline{H}$), 7.20-7.05 (2H,m, ArH), 6.71 (2H, d, *J* 8.4Hz,$Ar(OMe)_2\underline{H}$), 4.88-4.20 (4H, m, $NC\underline{H}_2S$ and 2 x α-CH), 3.75 (6H, s, OMe), 3.40-2.79 (4H,m, CH_2Ar and $SC\underline{H}_2CH$) and 2.07 (s) and 1.87 (s); together (3H,$COC\underline{H}_3$); *m/z* (ESI, 60V) 502 (MH^+).

EXAMPLE 48

***N*-Acetyl-*D*-thioproline (*N'*-benzoyl)-*L*-4-amino phenylalanine**

from (*N*-benzoyl)-*L*-4-amino phenylalanine methyl ester and *N*-acetyl-*D*-thioproline δH (DMSO-d^6,390K) 9.72 (1H, s,NH), 7.66 (2H,d,*J* 8.5Hz, ArH),7.68-7.49 (6H, m, ArH and NH), 7.19 (2H, d, *J* 8.5Hz, ArH), 4.85 (1H, dd, *J* 7.4, 3.9Hz, CHα-thiopro), 4.78 (1H, d, *J* 9.2Hz, $NC\underline{H}_AH_BS$), 4.55 (1H, ddd, *J* 8.2, 8.2, 5.5Hz, CHα-Ph), 4.39 (1H, d, *J* 9.2Hz, $NCH_A\underline{H}_BS$),3.27 (1H, dd, *J* 11.7, 7.4Hz, $SC\underline{H}_AH_BCH$), 3.13 (1H, dd, *J* 14.1, 5.4Hz, $C\underline{H}_AH_BAr$),3.06 (1H, dd, *J* 11.5, 3.9Hz, $SCH_A\underline{H}_BCH$), 2.99 (1H, dd, *J* 14.1, 8.2Hz, $CH_A\underline{H}_BAr$) and 2.01 (3H, s, $COCH_3$); *m/z* (ESI, 60V) 442 (MH^+).

EXAMPLE 49

N-Acetyl-D-thioproline-(N'-2,6-dimethylbenzoyl)-L-4-amino phenylalanine

from (*N*-2,6-dimethylbenzoyl)-*L*-4-amino-phenylalanine methyl ester and *N*-acetyl-*D*-thioproline δH (DMSO-d^6) 10.29 (1H, s, NH),8.44 (d, J 8.0Hz) and 8.15 (d, J 8.3Hz) together (1H, NH), 7.62 (2H, d, J 6.5Hz, ArH), 7.29-7.02 (5H, m, ArH), 4.86-4.18 (4H, m, NCH_2S and 2 x α-CH), 3.22-2.71 (4H, m, SCH_2CH and CH_2Ar), 2.26 (6H, s, CH_3) and 2.06 (s) and 1.84 (s) together (3H, $COCH_3$); m/z (ESI, 60V) 470 (MH^+).

EXAMPLE 50

N-Acetyl-D-thioproline-(N'-isonicotinoyl)-L-4-amino-phenylalanine

from (*N*-isonicotinoyl)-*L*-4-amino phenylalanine methyl ester and *N*-acetyl-*D*-thioproline δH (DMSO-d^6,390K,) 10.00 (1H, s, NH), 8.73 (2H, d, J 6.0Hz,ArH), 7.83 (2H, d, J 6.0Hz, ArH), 7.54 (2H,d,J 8.5Hz,ArH), 7.37 (1H, br s, NH), 7.17 (2H, d, J 8.5Hz, ArH), 4.85-4.73 (2H, m, NCH_2S), 4.36 (1H, d, J 9.3Hz, α-CH), 4,00 (1H, br s, α-CH), 3.22 1H, dd, J 11.3, 7.2Hz), 3.16-3.05 (2H,m), 3.10 (1H, dd, J 13.5,5.2Hz) and 1.96 (3H, s,$COCH_3$); m/z (ESI, 60V) 443 (MH^+).

EXAMPLE 51

N-Acetyl-D-thioproline-(N'-tert-butylcarbonyl)-L-4- amino phenylalanine

from (*N*-tert-butylcarbonyl)-*L*-4-amino phenylalanine methyl ester and *N*-acetyl-*D*-thioproline δH (DMSO-d^6) 9.10 (1H,s,NH), 8.40 (d, J 8.0Hz) and 8.10 (d, J 8.2Hz) together (1H, NH), 7.52 (2H, d,J 7.9Hz, ArH), 7.10 (2H, app.dd. J 9.3, 8.9Hz, ArH), 4.85-4.18 (4H, m, NCH_2S and 2 x α-CH), 3.29-2.76 (4H, m, CH_2Ar and SCH_2CH), 2.06 (s) and 11.5 (s) together (3H, $COCH_3$) and 1.21 (9H, s,^{t}Bu); m/z (ESI, 60V) 422 (MH^+).

EXAMPLE 52

N-Acetyl-D-thioproline-(N'-2,6-dichloropheylacetyl)-L-4-amino-phenylalanine

from (*N*-2,6-dichlorophenylacetyl)-*L*-4-amino phenylalanine methyl ester and *N*-acetyl-*D*-thioproline δH (DMSO-d^6) 10.22 (1H, s, NH), 8.42 (d, J 8.2Hz) and 8.12 (d, J 8.4Hz) together (1H, NH), 7.55-7.30 (5H, m, ArH),

7.13 (2H, dd, J 9.1, 9.1Hz,ArH), 4.87-4.14 (4H, m, NCH_2S and 2 x α-CH), 4.03 (2H, s,$COCH_2Ar$), 3.45-2.72 (4H, m,$CHCH_2Ar$ and SCH_2CH) and 2.05 (s) and 1.84 (s); together (3H, $COCH_3$); m/z (ESI, 60V) 524 (MH^+).

The following assays can be used to demonstrate the potency and selectivity of the compounds according to the invention. In each of these assays an IC_{50} value was determined for each test compound and represents the concentration of compound necessary to achieve 50% inhibition of cell adhesion where 100% = adhesion assessed in the absence of the test compound and 0% = absorbance in wells that did not receive cells.

$\alpha_4\beta_1$ Integrin-dependent Jurkat cell adhesion to VCAM-Ig

96 well NUNC plates were coated with $F(ab)_2$ fragment goat anti-human IgG Fcγ-specific antibody [Jackson Immuno Research 109-006-098: 100 μl at 2 μg/ml in 0.1M $NaHCO_3$, pH 8.4], overnight at 4°. The plates were washed (3x) in phosphate-buffered saline (PBS) and then blocked for 1h in PBS/1% BSA at room temperature on a rocking platform. After washing (3x in PBS) 9 ng/ml of purified 2d VCAM-Ig diluted in PBS/1% BSA was added and the plates left for 60 minutes at room temperature on a rocking platform. The plates were washed (3x in PBS) and the assay then performed at 37° for 30 min in a total volume of 200 μl containing 2.5×10^5 Jurkat cells in the presence or absence of titrated test compounds.

Each plate was washed (2x) with medium and the adherent cells were fixed with 100μl methanol for 10 minutes followed by another wash. 100μl 0.25% Rose Bengal (Sigma R4507) in PBS was added for 5 minutes at room temperature and the plates washed (3x) in PBS. 100μl 50% (v/v) ethanol in PBS was added and the plates left for 60min after which the absorbance (570nm) was measured.

$\alpha_4\beta_7$ Integrin-dependent JY cell adhesion to MAdCAM-Ig

This assay was performed in the same manner as the $\alpha_4\beta_1$ assay except that MAdCAM-Ig (150ng/ml) was used in place of 2d VCAM-Ig and a sub-line of the β-lympho blastoid cell-line JY was used in place of Jurkat cells.

The IC_{50} value for each test compound was determined as described in the $\alpha_4\beta_1$ integrin assay.

$\alpha_5\beta_1$ **Integrin-dependent K562 cell adhesion to fibronectin**

96 well tissue culture plates were coated with human plasma fibronectin (Sigma F0895) at 5µg/ml in phosphate-buffered saline (PBS) for 2 hr at 37°C. The plates were washed (3x in PBS) and then blocked for 1h in 100µl PBS/1% BSA at room temperature on a rocking platform. The blocked plates were washed (3x in PBS) and the assay then performed at 37°C in a total volume of 200µl containing 2.5x 10^5 K562 cells, phorbol-12-myristate-13-acetate at 10ng/ml, and in the presence or absence of titrated test compounds. Incubation time was 30 minutes. Each plate was fixed and stained as described in the $\alpha_4\beta_1$ assay above.

$\alpha_m\beta_2$**-dependent human polymorphonuclear neutrophils adhesion to plastic**

96 well tissue culture plates were coated with RPMI 1640/10% FCS for 2h at 37°C. 2 x 10^5 freshly isolated human venous polymorphonuclear neutrophils (PMN) were added to the wells in a total volume of 200µl in the presence of 10ng/ml phorbol-12-myristate-13-acetate, and in the presence or absence of test compounds, and incubated for 20min at 37°C followed by 30min at room temperature. The plates were washed in medium and 100µl 0.1% (w/v) HMB (hexadecyl trimethyl ammonium bromide, Sigma H5882) in 0.05M potassium phosphate buffer, pH 6.0 added to each well. The plates were then left on a rocker at room temperature for 60 min. Endogenous peroxidase activity was then assessed using tetramethyl benzidine (TMB) as follows: PMN lysate samples mixed with 0.22% H_2O_2 (Sigma) and 50µg/ml TMB (Boehringer Mannheim) in 0.1M sodium acetate/citrate buffer, pH 6.0 and absorbance measured at 630nm.

$\alpha IIb/\beta_3$ **-dependent human platelet aggregation**

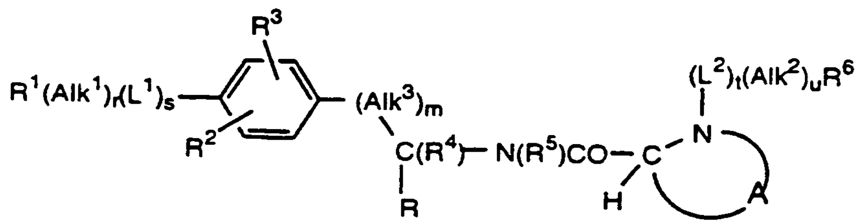
Human platelet aggregation was assessed using impedance aggregation on the Chronolog Whole Blood Lumiaggregometer. Human platelet-rich plasma (PRP) was obtained by spinning fresh human venous blood anticoagulated with 0.38% (v/v) tri-sodium citrate at 220xg for 10 min and diluted to a cell density of 6 x 10^8/ml in autologous plasma. Cuvettes

contained equal volumes of PRP and filtered Tyrode's buffer (g/liter: NaCl 8.0; $MgCl_2.H_2O$ 0.427; $CaCl_2$ 0.2; KCl 0.2; D-glucose 1.0; $NaHCO_3$ 1.0; $NaHPO_4.2H_2O$ 0.065). Aggregation was monitored following addition of 2.5μM ADP (Sigma) in the presence or absence of inhibitors.

In the above assays the compounds of the invention generally have IC_{50} values in the $\alpha_4\beta_1$ and $\alpha_4\beta_7$ assays of 1 μM and below. The compounds of the Examples typically had IC_{50} values of 500nM and below in these assays. In the other assays featuring α integrins of other subgroups the same compounds had IC_{50} values of 50μM and above thus demonstrating the potency and selectivity of their action against α_4 integrins.

CLAIMS

1. A compound of formula (1)



(1)

wherein

R^1 is a hydrogen atom or an optionally substituted cycloaliphatic, polycycloaliphatic, heterocycloaliphatic, polyheterocycloaliphatic, aromatic or heteroaromatic group;

Alk^1 and Alk^2, which may be the same or different, is each an optionally substituted aliphatic or heteroaliphatic chain;

L^1 is a linker atom or group;

r, s, t and u is each zero or an integer 1;

Alk^3 is a straight or branched alkylene chain;

m is zero or an integer 1;

R^4 is a hydrogen atom or a methyl group;

R^5 is a hydrogen atom or a straight or branched alkyl group;

A is a chain $-[C(R^7)(R^8)]_pY[C(R^9)(R^{10})]_q-$ in which Y is a sulphur atom or a -S(O)- or $-S(O)_2-$ group, R^7, R^8, R^9 and R^{10}, which may be the same or different, is each a hydrogen atom or a straight or branched alkyl or optionally substituted aromatic group, or R^7 and R^8 together with the carbon atom to which they are attached, or R^9 and R^{10} together with the carbon atom to which they are attached, each forms a C_{3-7}cycloalkyl group, and p and q, which may be the same or different, is each zero or an integer 1 or 2, provided that when one of p or q is zero the other is an integer 1 or 2;

L^2 is a linker group selected from -C(O)-, -C(O)O-, -C(S)-, $-S(O)_2-$, $-CON(R^{11})-$, [where R^{11} is a hydrogen atom or a straight or branched alkyl group], $-CSN(R^{11})-$, $-SON(R^{11})-$ or $SO_2N(R^{11})-$;

R^2 and R^3, which may be the same or different is each an atom or group $-L^3(CH_2)_pL^4(R^{2a})_q$ in which L^3 and L^4 is each a covalent bond or a linker atom or group, p is zero or the integer 1, q is an integer 1, 2 or 3 and R^{2a} is a hydrogen or halogen atom or a group selected from straight or branched alkyl, $-OR^{12}$ [where R^{12} is a hydrogen atom or an optionally substituted straight or branched alkyl group], $-SR^{12}$, $-NR^{12}R^{13}$, [where R^{13} is as just defined for R^{12} and may be the same or different], $-NO_2$,-CN, $-CO_2R^{12}$, $-SO_3H$, $-SO_2R^{12}$, $-OCO_2R^{12}$, $-CONR^{12}R^{13}$, $-OCONR^{12}R^{13}$, $-CSNR^{12}R^{13}$, $-COR^{12}$, $-N(R^{12})COR^{13}$, $N(R^{12})CS^{13}$, $-SO_2N(R^{12})(R^{13})$, $-N(R^{12})SO_2R^{13}$, $-N(R^{12})CONR^{13}R^{14}$ [where R^{14} is a hydrogen atom or an optionally substituted straight or branched alkyl group], $-N(R^{12})CSNR^{13}R^{14}$ or $-N(R^{12})SO_2NR^{13}R^{14}$;
R is a carboxylic acid or a derivative thereof;
R^6 is a hydrogen atom or an optionally substituted cycloaliphatic, polycycloaliphatic, heterocycloaliphatic, polyheterocycloaliphatic, aromatic or heteroaromatic group, provided that:
(1) when $R^1(Alk^1)_r(L^1)_s$- is $R^1(Alk^1)_rO$-, $R^1(Alk^1)_rC(O)O$-, $R^1(Alk^1)_rNHC(O)O$- or $R^1(Alk^1)_rS(O)_2O$-, [in which R^1 is a hydrogen atom or an optionally substituted aromatic group and Alk^1 is an optionally substituted alkyl group] and $R^6(Alk^2)_u(L^2)_t$- is $R^6(Alk^2)_uCO$-, $R^6(Alk^2)_uC(O)O$-, $^6(Alk^2)_uNHCO$- or $R^6(Alk^2)_uS(O)_2$- [in which Alk^2 is an optionally substituted alkyl chain], then R^6 is an optionally substituted cycloaliphatic, polycycloaliphatic, hetercycloaliphatic or heteroaromatic group; and
(2) Alk^2,when present is not a $-(CH_2)_nS$-, $-(CH_2)_nSS$- or $-(CH_2)_nSC(O)$- chain, where n is an integer 1, 2 or 3;
and the salts, solvates and hydrates thereof.

2. A compound according to Claim 1 in which R is a $-CO_2H$ group.

3. A compound according to Claim 1 or 2 in which Alk^3 is a $-CH_2$- chain and m is an integer 1.

4. A compound according to any one of Claims 1 to 3 in which R^4 and R^5 is each a hydrogen atom.

5. A compound according to any one of Claims 1 to 4 in which the chain A is a $-C(R^7)(R^8)SC(R^9)(R^{10})-$ chain.

6. A compound according to any one of Claims 1 to 5 in which R^1 is an optionally substituted aromatic or heteroaromatic group.

7. A compound according to Claim 6 in which R^1 is an optionally substituted phenyl, pyridyl or pyrimidyl group.

8. A compound according to anyone of Claims 1 to 7 in which t is an integer 1.

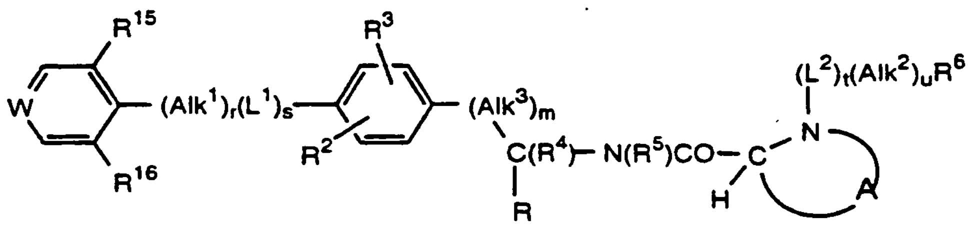
9. A compound according to any of the preceding Claims in which $R^1(Alk^1)_r(L^1)_s-$ is a $R^1CH_2L^1$ or R^1L^1 group where R^1 is an optionally substituted aromatic or heteroaromatic group, Alk^3 is a $-CH_2-$ chain, m is an integer 1, R is a $-CO_2H$ group, R^4 and R^5 is each a hydrogen atom and $-(L^2)_t(Alk^2)_uR^6$ is a $-L^2CH_2R^6$ group where R^6 is a hydrogen atom or an optionally substituted aromatic or heteroaromatic group.

10. A compound according to Claim 9 in which $R^1(Alk^1)_r(L^1)_s-$ is a $R^1CSN(R^{11})-$, $R^1N(R^{11})-$, $R^1N(R^{11})CO-$, $R^1N(R^{11})CS-$, $R^1S(O)N(R^{11})-$, $R^1S(O)_2N(R^{11})-$, $R^1N(R^{11})SO-$, $R^1N(R^{11})S(O)_2-$ or $R^1CON(R^{11})-$ group.

11. A compound according to Claim 10 wherein $R^1(Alk^1)_r(L^1)_s-$ is a $R^1CON(R^{11})-$ group.

12. A compound according to any one of Claims 9 to 11 wherein R^6 is an optionally substituted heteroaromatic group.

13. A compound according to Claim 1 which has the formula (1a):



(1a)

wherein -W= is -CH= or -N=; R^{15} and R^{16},which may be the same or different, is each an atom or group $-L^3(CH_2)_pL^4(R^{2a})_q$ as defined for R^2 and R^3 in Claim (1); Alk^1, r, L^1,s, R^2, R^3, Alk^3, m, R, R^4, R^5, A, L^2, t, Alk^2, u and R^6 are as defined in Claim (1); and the salts, solvates,hydrates and N-oxides thereof.

14. A compound according to Claim 13 wherein R is a $-CO_2H$ group, Alk^3 is a $-CH_2-$ chain, m is an integer 1, R^4 and R^5 is each a hydrogen atom, $-(L^2)_t(Alk^2)_uR^6$ is a $L^2CH_2R^6$ group where R^6 is a hydrogen atom or an optionally substituted aromatic or heteroaromatic group and the chain A is a $-C(R^7)(R^8)SC(R^9)(R^{10})-$ chain.

15. A compound according to Claim 13 or Claim 14 wherein $(Alk^1)_r(L^1)_s$ is a $-SO_2NH-$, -C(O)O-, -NH- or -CONH- group.

16. A compound according to any one of Claims 13 to 15 wherein each of R^{15} and R^{16} is a substituent $-L^3(CH_2)_pL^4(R^{2a})_q$ in which R^{2a} is not a hydrogen atom when L^3 and L^4 is each a covalent bond and p is zero.

17. A compound which is:
N-(Pyrid-3-ylacetyl)-*D*-thioproline-(*N*-2,6-dichlorobenzoyl)-*L*-4-aminophenylalanine;
N-Acetyl-*D*-thioproline-(*N*-3,5-dichloroisonicotinoyl)-*L*-4-amino phenylalanine;
N-(Pyrid-3-ylacetyl)-*D*-thioproline-*O*-(2,4,6-trichlorobenzyl)-*L*-tyrosine;
N-(Pyrid-3-ylacetyl)-*D*-thioproline-(*O*-2,4,6-trichlorobenzoyl)-*L*-tyrosine;
N-(Pyrid-3-ylacetyl)-*D*-thioproline-(*O*-2,6-dichlorobenzoyl)-*L*-tyrosine;

N-Acetyl-*D*-thioproline-(*N'*-2,6-dichlorobenzoyl)-*L*-4-aminophenylalanine;
N-Acetyl-*D*-thioproline-[*N'*-2-fluoro-6-(trifluoromethyl)benzoyl]-*L*-4-aminophenylalanine;
N-Acetyl-*D*-thioproline-(*N'*-2,4,6-trichlorobenzoyl)-*L*-4-aminophenylalanine;
N-Acetyl-*D*-thioproline-(*N'*-2,6-trichlorobenzyl)-*L*-4-aminophenylalanine;
and the salts, solvates, hydrates and N-oxides thereof.

18. A pharmaceutical composition coprising a compound according to Claim 1 together with one or more pharmaceutically acceptable carriers, excipients or diluents.